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CYANOSIS

BY
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AND
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PREFACE

The significance of cyanosis, its importance in the diagnosis, treatment, and prognosis of many diseases, particularly those of the circulatory and respiratory organs, has been the subject of considerable investigation. However, an analysis of the physiological causes underlying this conspicuous symptom has not been undertaken. During the past few years new facts have accumulated bearing directly and indirectly on the conception of cyanosis. The authors have attempted to interpret these facts from a physiological as well as from a historical standpoint. Viewpoints concerning the quantitative influence of the different factors involved in the production of cyanosis have been correlated with the earlier bedside observations, and the attempt has been made to indicate in certain clinical conditions the physiological abnormalities associated with the development of the cyanotic color.

C.L.
D.D.V.S.

New York,
November 20, 1922.

CYANOSIS

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INTRODUCTION

Cyanosis (from the Greek κύανος, meaning dark blue) indicates, as is well known, a blue or bluish color of the skin, of the mucous membranes, and of other organs, the retina, spleen, liver, kidneys, etc., usually not visible. To its presence or absence importance has been attributed in the differential diagnosis, the functional diagnosis, and the prognosis of various diseases. Since cyanosis through bedside observation was clearly recognized as a definite pathological phenomenon and in the middle of the eighteenth century through combination of clinical observations and morbid anatomy was ascribed to various pathological anatomic disturbances, it has been explained in many different ways. It has been ascribed to admixture of venous and arterial blood, to stasis in the systemic circulation, to polycythemia, and to overloading of the blood with carbon dioxide. It has figured as a disease in itself (morbus cæruleus)[1] and as a symptom of other diseases. Special therapeutic procedures (oxygen inhalation, venesection) have often been used against it.

DEGREE, DISTRIBUTION, AND SHADE OF CYANOTIC COLOR

The coloration of cyanosis is diffuse like the coloration of anemia and icterus. It may be generalized, but is usually more marked in some regions than in others. In most cases, however, the cyanotic color is found only in certain regions; lips, nose, cheeks, ears, hands, and feet. The intensity of cyanosis may vary from a just perceptible blue color to almost black. Similarly, the shade of the color may differ as indicated by the original names used to describe it. It has been called ictère bleue, ictère violet, mélasictère, maladie bleue,

[1] "La cyanose est une maladie constituée par l'introduction du sang veineux dans le système artériel général, en vertu de communications ouvertes, soit entre les cavités droites et gauches du cœur, soit entre les principaux troncs vasculaires: maladie qui est accompagnée de la coloration bleuâtre, livide, de la peau et des membranes muqueuses" (Gintrac, 1824, p. 7).

and cyanopathie, before Baumes introduced the present name in 1801. More recent writers have used the terms leaden blue, cherry-red-blue (Stadie, a), heliotrope, or lilac (Abrahams, Hallows, and French). The heliotrope color has thus far been observed only in connection with severe lung involvement, particularly in influenzal pneumonia. It is in many cases not easy to decide whether or not a cyanotic skin color is present, and it is also difficult to compare the intensity of cyanosis in different cases or in different regions. An oxyhemoglobinometer by means of which the intensity or shade of the cyanotic color could be matched has recently been devised by Flagg. It consists of a color wheel by means of which varying percentages of light and dark red can be mixed. So far the method has not been applied to cases other than patients with cyanosis resulting from anesthesia.

CAUSE OF CYANOTIC COLOR

As in anemia, the essential cause of the coloration of cyanosis is a change in the character of the circulating blood. In this respect it differs from icterus, the causative factors of which are present not only in the blood but also in the intervascular tissues. For this reason the icteric color is often most pronounced in the sclera, where the capillaries are very few and united at intervals so wide that a diffuse cyanotic color can hardly be produced. For the same reason cyanosis, unlike icterus, disappears when the blood is pressed out of the skin.

The blood component responsible for the production of the cyanotic color is that portion of the hemoglobin which is not in the state of oxyhemoglobin, but is either normal reduced hemoglobin, or methemoglobin, or sulfhemoglobin.[2] In this paper we are considering

[2] The autotoxic enterogenous type of cyanosis was the name given by Stokvis (1902) to a condition of cyanosis in a patient suffering from enteritis. Stokvis could demonstrate spectroscopically the presence of methemoglobin in the blood. Similar observations were at the same time published by Talma. Stokvis and Talma ascribed the occurence of cyanosis to the presence of methemoglobin. Cf. cyanosis in cholera morbus.

However, it is clear that the mere qualitative demonstration of methemoglobin or sulfhemoglobin in the blood of such patients even if it is very suggestive, is not sufficient to exclude other causes. The same applies to Hijmans van den Bergh's conclusions. Quantitative determinations, not only of the methemoglobin and sulfhemoglobin, but also of the amount of ordinarily reduced hemoglobin, are, therefore, required before any definite conclusions can be drawn.

cyanosis due only to increased oxygen unsaturation of the blood, i.e., to an increased amount of reduced hemoglobin.[3] The amount of reduced hemoglobin, or the volume per cent of oxygen unsaturation of the blood,[4] must reach a certain value before cyanosis appears. This is in part, of course, due to the fact that a certain proportion of blue must be mixed with the red in order to change appreciably the blood color, but it appears to be due chiefly to the opacity of the epidermis, by reason of which, a certain intensity of blue color is required in the corium in order to show through. *For this reason cyanosis appears to be chiefly dependent on the absolute concentration of reduced hemoglobin in the blood, rather than on the ratio of reduced to oxygenated* (Lundsgaard, 1919). About 5 grams of reduced hemoglobin per 100 c.c. of capillary blood appear necessary to cause cyanosis, the amount of oxygenated hemoglobin also present having relatively little effect. An anemic with less than 5 grams of hemoglobin per 100 c.c. of blood cannot usually become cyanotic.

It is the blood in the capillaries, and possibly in the arterioles and venules of the subpapillary plexus as well, which produces the cyanotic skin color. The arteries and most of the veins are so far away from the skin that their content cannot influence the skin color. A few veins, to be sure, are situated superficially enough to influence markedly the skin color, but they are too few and too far apart to cause any diffuse coloration. A blue color confined to the skin over the superficial veins is therefore not termed cyanosis.

The fact that the oxygen content of the blood changes during its passage through the capillaries, every section of which may influence

[3] Cyanosis should not be confused with anoxemia, which indicates a condition where there is, for some reason or other, an oxygen want in the tissue cells. Anoxemia may be present without cyanosis, and cyanosis may be present without the appearance of any anoxemic symptoms.

"The word 'anoxæmia' should evidently be taken as signifying a condition in which the *free* oxygen in the systemic capillary blood is abnormally diminished;" (Haldane, Respiration, p. 124).

[4] It is convenient to express reduced hemoglobin concentration in terms of oxygen unsaturation, since oxygen values are those experimentally determined. One cubic centimeter of oxygen combines with 0.75 gram of hemoglobin. So that 5 grams of reduced hemoglobin may be expressed as $\frac{5}{0.75} = 6.7$ volumes per cent of oxygen unsaturation. "Volumes per cent" expresses, as usual, cubic centimeters of a gas in 100 c. c. of a fluid.

the skin color, makes it difficult to find an exact quantitative expression for the threshold value of oxygen unsaturation causing cyanosis.[4] It cannot be expressed solely by the amount of oxygen unsaturation at the arterial ends of the capillaries, nor solely by the unsaturation at the venous ends. If the arterial unsaturation is A, and the venous V, the values for the capillary unsaturation, C, must change from A to V during the passage of the blood through the capillaries. The average of the successive sections of a capillary will give an unsaturation larger than A and smaller than V. Lundsgaard (c) has expressed the mean capillary unsaturation as $\frac{A+V}{2}$, that is, the mean between arterial and venous unsaturations. He found in a series of cases that cyanosis appeared when the mean capillary unsaturation $\frac{A+V}{2}$ approximated 6 to 7 volumes per cent, which corresponds to about 5 grams of reduced hemoglobin per 100 c.c. of blood. This he called the threshold value for the appearance of cyanosis.

MODIFYING FACTORS OF CYANOSIS

While oxygen unsaturation of the capillary blood is, it appears certain, the essential cause of cyanosis, there are modifying factors which affect the resulting coloration, and which probably vary the threshold concentration of reduced hemoglobin in the capillary blood necessary to produce visible cyanosis. Such factors may also considerably change the intensity of cyanosis caused by a given amount of oxygen unsaturation.

The principal factors appear to be (1) the thickness of the epidermis (which in itself has no vessels); (2) the normal or pathological pigment of the skin (in sunburnt people, in the black and yellow races, in patients suffering from icterus, from Addison's disease, from argyria, etc.); (3) normal and pathological variations in the color of the blood plasma (varying concentration of normal and abnormal pigments in the plasma, variations in lipoid content, etc.; here may also be included a possible effect of large increase in the leucocytes, as in leucemia); (4) variations in the concentration of oxidized hemoglobin in the blood; (5) variations in number, width, and length of blood-filled capillaries in a given surface area; (6)

variations in the extent to which the average capillary blood approximates in its unsaturation more nearly the arterial than the venous blood or vice versa. *These modifying factors cannot, however, produce cyanosis themselves; they can influence the amount of oxygen unsaturation necessary to give the skin a perceptible blue color, and can modify the shade of color produced.*

Not much information is at hand as to the influence on cyanosis of any of the above enumerated six factors, and certainly not any information which allows a quantitative discussion of the problem. The influence of the first two factors, the thickness of the epidermis and the skin pigment, is evident. They are partly responsible for variations in shade and intensity of cyanotic color in different regions of the body and in different individuals. Being fairly constant features over a long period of time, these factors cannot be responsible for transitory variations in cyanotic color in a given region. The third factor, the color of the plasma, does not vary from one region of the body surface to another, nor does it vary much over a short period of time. If this factor has any appreciable influence on the cyanotic color, it can cause only slight modifications in the color (probably most in the shade of the color) present in different individuals. The influence of the fourth factor, the concentration of oxyhemoglobin in the blood, is not easy to analyze. From observations of patients and from blood analyses in different individuals (Lundsgaard, c), in whom the hemoglobin concentration varied over a wide range (anemic and polycythemic patients), one cannot decide whether the degree of cyanosis varies in direct or in inverse proportion to the concentration of oxyhemoglobin. It appears that the influence of this factor is relatively smaller than one might expect.

The variations in number, width, and length of blood-filled capillaries per unit of skin (or surface) area, undoubtedly rank high in importance. Due to variations in these factors the same concentration of reduced hemoglobin in the capillaries may produce a cyanotic color of varying intensity in different individuals, in different skin regions of the same individual, and at different times. During the last few years our knowledge of the anatomy and physiology of the capillary system has increased considerably.

This is mainly due to two circumstances: first, to the method for direct microscopic examination in vivo of the skin capillaries

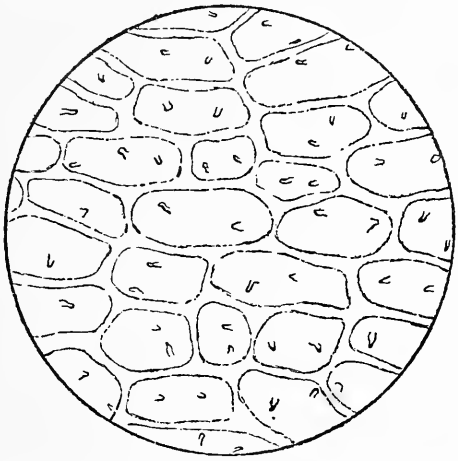

FIG. 1. CAPILLARIES FROM THE SKIN OF THE FIRST PHALANX OF THE FINGER NEAR THE METACARPOPHALANGEAL JOINT (AFTER WEISS AND HOLLAND)

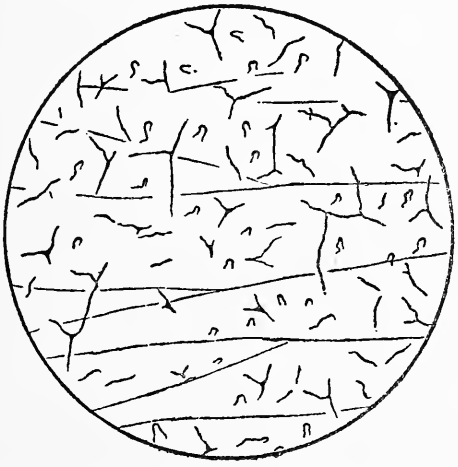

FIG. 2. CAPILLARIES FROM THE BACK OF THE HAND. A FEW DEEPER VENULES ARE SEEN (AFTER WEISS AND HOLLAND)

ingeniously devised by Lombard (1912) and Weiss (1916); second, to definite indirect (Dale) and direct (Krogh) proof of the existence of a capillary motor function independent of the other parts of the

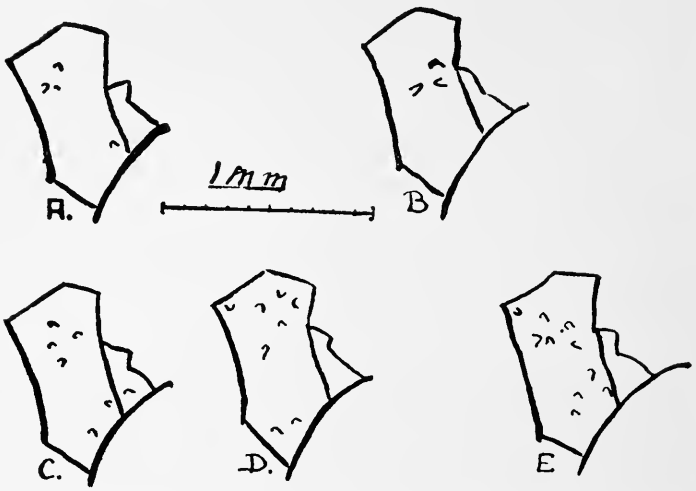

FIG. 3. THE DIAGRAMS A, B, C, D, AND E GIVE THE NUMBER OF OPEN CAPILLARIES IN THE SAME AREA FROM THE BACK OF THE HAND OBSERVED AT VARIOUS TIMES OVER A PERIOD OF 4 DAYS (AFTER CARRIER)

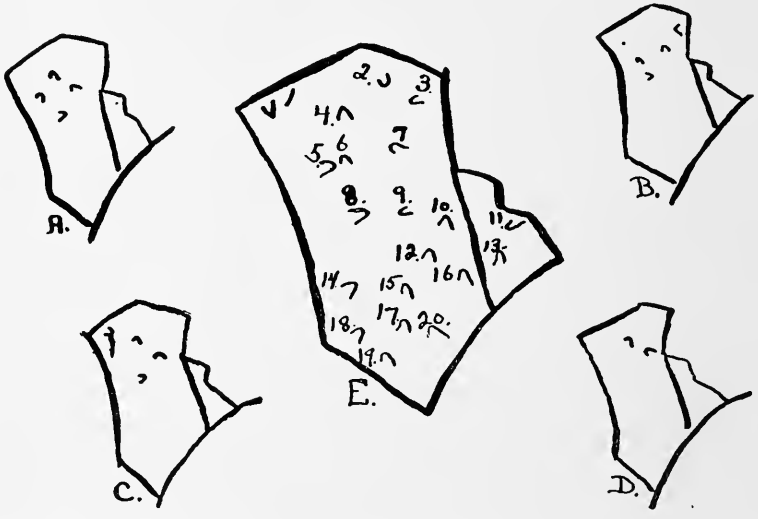

FIG. 4. DIAGRAMS A, B, C, D, AND E GIVE THE NUMBER OF OPEN CAPILLARIES IN THE SAME AREA AS IN FIG. 3 AT DIFFERENT OBSERVATIONS OVER A PERIOD OF 13 MINUTES. DIAGRAM E IS DRAWN TWICE THE SIZE OF THE OTHER FIGURES AND EACH CAPILLARY IS GIVEN A NUMBER. IN E ALL THE CAPILLARIES ARE OPEN AS A RESULT OF LIGHT PRESSURE (AFTER CARRIER)

vascular system. We shall briefly discuss a number of facts which are of importance to our problem even though their quantitative relationship to production of cyanosis cannot yet be worked out.

Variations in the number, width, and length of the skin capillaries in normal subjects under natural conditions. Weiss and Holland have given a detailed description and several illustrations of the variations in density of the capillary network in various regions of the skin. Figures 1 and 2 illustrate the difference in the capillaries in the skin over the first phalanx of the finger (fig. 1), and the back of the hand (fig. 2). At the last place a few deep venules are observed between the capillaries. Such variations are found, however, not only at different regions of the skin, but also in the same skin region at even very short intervals of time, as demonstrated by Carrier (figs. 3 and 4). This is due to the opening (term introduced by A. Krogh, 1919, b) of a varying number of capillaries by the independent capillary motor function. The observations on which figures 3 and 4 are based were made on the back of the hand. In the wall at the finger-nail the number of opened up capillaries is much more constant, indicating probably that nearly all the capillaries normally are open. (Carrier, p. 535.) However, great variations in number, shape, width, and length of the capillaries of the nail wall take place from one individual to another and from one finger to another, as shown by Rosenberger, Schur, Moog and Ehrmann, and Secher. Figures 5, 6, 7, and 8 are taken from Secher's publication and show this very clearly. The observations were made on individuals in whom one might expect normal conditions.

Variations in the number, width, and length of the capillaries in abnormal and in pathological conditions. To the above mentioned variations, found in normal or presumably normal subjects under normal conditions, may be added even larger but not yet well defined variations found, after application of stimuli to the skin, or in disease. Of particular interest for our problem is the effect of thermic stimuli, by means of which cyanosis, as is well known, can be produced. The morphological and functional changes which take place in the capillaries after thermic stimuli and give rise to varying skin colors (erythrosis, cyanosis) are described by Bruns and König and Carrier and will be considered more in detail in the chapter on

acrocyanosis. If stasis is applied to an arm, by means of von Recklinghausen's manchette for instance, it is easily demonstrated that not only does the number of blood-filled capillaries increase, but their

Fig. 5 Fig 6

Fig. 7 Fig. 8

FIGS. 5 TO 8. CAPILLARIES AT THE WALL OF THE NAIL IN DIFFERENT INDIVIDUALS IN WHOM NO CHANGES IN THE CAPILLARY NETWORK SHOULD BE EXPECTED (AFTER SECHER)

length and particularly their width increase as well. Another result of the stasis is that a few deeper, small vessels become visible. Similar and undoubtedly similarly caused conditions are observed in many

heart patients with increased venous pressure. The cause of the increase in the size and number of visible capillaries in these cases of cyanosis is undoubtedly the increase in the local blood volume, whereas in the cyanosis caused by cold the increased amount of blood is secondary to a dilatation or paralysis of the capillaries. Also in

FIG. 9. CAPILLARIES IN A NORMAL INDIVIDUAL. NAIL WALL (AFTER BOAS)

polycythemic patients (including some of the congenital heart lesions) an increase in the number and width of the capillaries is observed. Associated with this is an increase in the total blood volume as shown by Bock and Means. Probably there is also a hyperplastic condition of the capillary system. In acrocyanosis of different origin, increased width and length of the capillaries have been found by Weiss and Holland; Henius; Halpert; and Boas. Figures 9 and 10, which

are from Boas' publication, illustrate the difference between the capillaries of a normal individual and of a patient with acrocyanosis of unknown etiology. In artificial stasis, in heart diseases with stasis, in acrocyanosis, and in polycythemic plethora, conditions therefore exist which increase the influence of one of the modifying factors, viz., the proportion of skin capillaries that are filled with blood, and the degree to which the capillaries are distended.

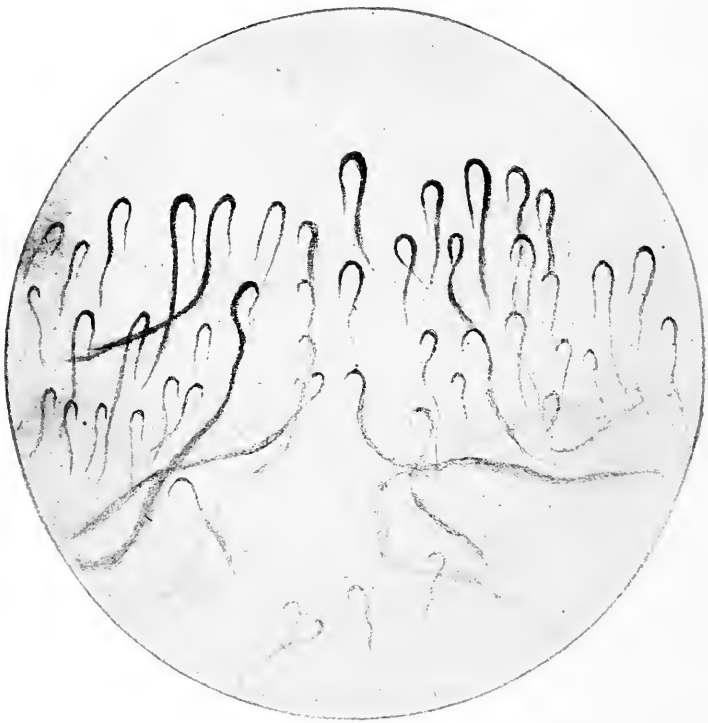

FIG. 10. CAPILLARIES FROM A PATIENT WITH ACROCYANOSIS. NAIL WALL (AFTER BOAS). FIGS. 9 AND 10 WERE MADE ON THE SAME SCALE

In pernicious anemia (but not in chlorosis) the opposite conditions have been observed by Schur, Jürgensen, and particularly by Hisinger-Jägerskiöld. Not only is the number of blood-filled capillaries fewer but they are thinner than usual. Hisinger-Jägerskiöld has observed that the venous part of the capillary loop and the "Schaltstück" (Jürgensen) are not broader than the arterial, as

they usually are under normal conditions. The principal cause of this condition is possibly a decrease in the total blood volume of the body. The scarcity and slenderness of the skin capillaries are usually proportional to the degree of anemia. In a few instances of cured pernicious anemia (Bothriocephalus anemia) Hisinger-Jägerskiöld found the same conditions as in the anemic stage. This led him to suggest the possibility of a hypoplastic development of the capillary system in these patients. In such cases the effect of the modifying factor is to diminish the influence of the blood on skin color and to decrease the tendency to cyanosis. It would be desirable in order to ascertain the relative importance of this factor in modifying the color produced by capillary unsaturation, to obtain in normal and cyanotic individuals information not only about the number and width of the capillaries for a given skin area but also about the increase in the number and width for a given increase in venous and capillary pressure, because an increased venous pressure is common in many cyanotic patients with circulatory disturbances.

The last mentioned factor, *the shape of the reduction curve of the oxyhemoglobin during the passage of the blood through the tissue capillaries* is probably also important. Unfortunately, little is known about it, and it does not seem very likely that much information on the question can be obtained.

If we assume the mean capillary unsaturation $\frac{A+V}{2}$ as the average unsaturation of the capillary blood, it is obvious that this is only an approximation. Certain factors tend to make the greater part of the capillary blood approximate the venous, while others tend to make it approximate the arterial. The value $\frac{A+V}{2}$ would represent exactly the average capillary unsaturation only if the blood in passing through each capillary lost a constant amount of oxygen per unit of capillary length traversed (i.e., losing one-fourth of the total oxygen loss in passing the first one-fourth of the capillary's length, etc.). This behavior would be represented by the straight line I (fig. 11).

It is quite certain that the straight line I does not exactly represent the conditions existing in the capillaries. When the arterial blood first enters the capillary, the oxygen tension difference between the

capillary blood and the tissues is greatest, and it becomes increasingly less as the blood progresses along the capillary towards the venous end. This factor would tend to make oxygen loss most rapid at the arterial end of the capillary and least at the venous, the course of oxygen loss being represented by a concave curve, like III (fig. 11). However, another factor tends to have the opposite effect, namely the form of the oxygen dissociation curve of the blood (Barcroft, a, p. 65). Because of this form, as the oxygen tension falls from arterial to venous, each succeeding given drop in tension results in a greater loss of oxygen content than the preceding. Thus, with 40 mm. CO_2 tension, Barcroft's blood in falling from 100 to 80 mm. oxygen tension, lost only about 2 per cent of its maximum total oxygen, whereas falling from

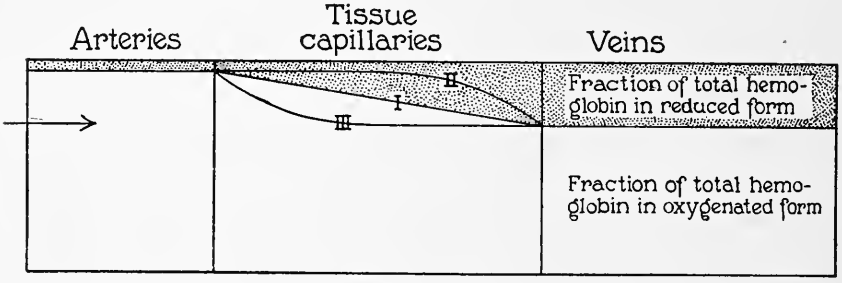

FIG. 11. DIAGRAM SHOWING HYPOTHETICAL VARIATIONS IN THE SHAPE OF THE REDUCTION CURVE OF OXYHEMOGLOBIN DURING THE PASSAGE OF THE BLOOD THROUGH TISSUE CAPILLARIES

40 to 20 mm. it lost about 40 per cent. This factor will tend to make the curve of oxygen loss along the capillary assume the form II, the most rapid loss occurring toward the venous end, at the lowest oxygen tensions. A third factor is the influence of carbonic acid. Because of the interaction of CO_2 and O_2 (Bohr; Christiansen, Douglas, and Haldane; L. J. Henderson; D. D. Van Slyke), CO_2 entering the capillaries from the tissues must react with the hemoglobin and thereby raise the oxygen tension. This effect would presumably tend to give a course of oxygen loss following curve III. Furthermore, low velocity of capillary flow, as directly observed by capillaroscopy in several instances of acrocyanosis (Carrier, Boas, and others), might be expected to result in most of the oxygen loss occurring near the arterial end of the capillary (curve III).

If the combined effect of all factors results in most rapid loss of oxygen in the arterial end of the capillary (curve III), then the greater part of the capillary blood will approximate the venous in oxygen content, and the formula expressing the average unsaturation of the capillary blood, instead of simply $\frac{A + V}{2}$, will be $\frac{A + nV}{1 + n}$, n being greater than 1. If, on the other hand, loss of oxygen is most rapid at the venous end of the capillary (curve II), the average capillary blood will be more nearly arterial than venous, and n of the above formula will be less than 1. Since it is impossible from data now available to know what condition prevails, we have, in relating cyanotic color to the content of reduced hemoglobin in the capillary blood, assumed the simplest relation, namely that $n = 1$, and the average unsaturation of the capillary blood is midway between that of the arterial and venous bloods respectively (curve I).

FACTORS INFLUENCING THE CONCENTRATION OF REDUCED HEMOGLOBIN IN THE CAPILLARY BLOOD

There are certain factors concerning which, unlike the above, we are able to obtain more or less exact information, and whose influence on the mean capillary unsaturation can be predicted with some degree of numerical accuracy. We shall briefly outline these factors in the following paragraphs, and in figures 12, 13, 14, and 15.

Figure 12 represents the circulatory conditions in a normal resting individual. The width of the band represents 20 volumes per cent of oxygen capacity (i.e., 15 grams of hemoglobin per 100 c.c. of blood, footnote 4, p. 8). The blood emerging from the lungs is 95 per cent saturated, contains 19 volumes per cent of oxygen, and has an unsaturation of 1 volume per cent. In passing through the tissue capillaries, the blood loses 5 volumes per cent of oxygen, and emerges with 14 volumes per cent of oxygen[5] and 6 volumes per cent of

[5] The oxygen normally present in the venous blood (about 14 volumes per cent) has been termed the reserve oxygen (Lundsgaard, 1919, e). It is in some ways to be looked upon as analogous to the reserve power of the heart. Its significance for the efficiency of the circulation is not yet clearly understood. According to observations of Lundsgaard and Möller (a) it appears possible that the reserve oxygen is taken into use during exercise not only in the working organs themselves, but through vasomotor action also in the resting parts of the body. This may be of importance for the topographic distribution of cyanosis as will be discussed later.

unsaturation. The mean unsaturation, C, of the capillary blood is $C = \frac{1 + 6}{2} = 3.5$ volumes per cent. The saturation of the blood with oxygen in the lungs is represented in our diagram by a straight line, although it is unlikely that this represents the actual course of

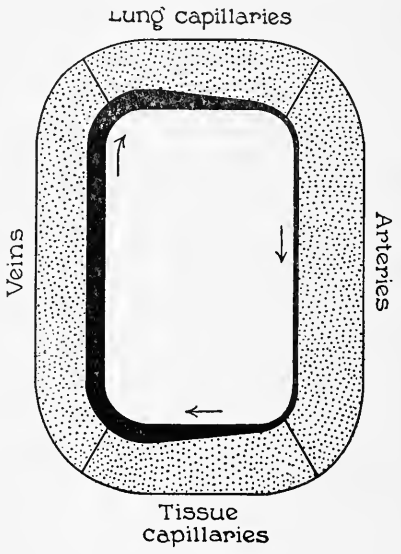

Fig. 12

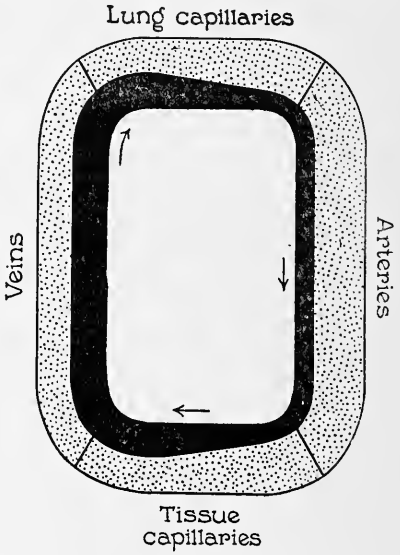

Fig. 13

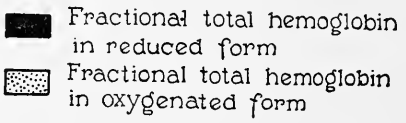

Fig. 12. Diagram Showing the Proportion of Oxygenated Hemoglobin to Reduced Hemoglobin in Different Parts of the Circulatory System in Normal Resting Individuals

Fig. 13. Diagram Showing the Proportion of Oxygenated to Reduced Hemoglobin in Different Parts of the Circulatory System in a Case of Incomplete Oxygenation in Aerated Parts of the Lungs

resaturation. For the present considerations this is, however, of no moment.

The arterial blood has, of course, the same composition in all the arteries, and we are correct in representing the arterial stream by a band of uniform width (figs. 12 to 15). The proportion between reduced

and oxidized hemoglobin, viz., 1 to 19, is indicated to be the same at all points of the arterial stream. Such constancy does not hold true for the venous blood; blood coming from different regions into different veins is reduced in different degrees. In spite of this fact, we have represented the venous blood stream in figures 12 to 14 by a single band which gives the average composition of the venous blood as we find it in the central veins. Figure 15 indicates how the venous blood from different parts may be of different composition. Because of this variation local cyanosis may occur where high local deoxidation causes a greater mean capillary unsaturation than the average.

Figures 13 and 14 distinguish between two conditions which lower the oxygen saturation of the arterial blood. Figure 13 represents a condition in which, although all the blood in passing from the right heart to the left traverses lung tissue anatomically accessible to inspired air, the diffusion of oxygen from the inspired air into the blood is so hindered that oxygenation is incomplete. Conditions causing such hindrance may be classified as (1) those involving low oxygen tension in the alveoli (high altitude, inefficient ventilation), and (2) those retarding diffusion of oxygen from the alveoli into the blood. Such retardation would depend on a decreased diffusion rate of oxygen through the alveolar walls.

Of the two causes mentioned of low alveolar oxygen tension, altitude requires no discussion. The rôle of inefficient ventilation is not so obvious. However, it appears self-evident that extremely shallow respiration, such that the inspired air is hardly more than enough (about 150 c.c.) to fill the dead space, must leave the gas exchange between alveoli and external air to be accomplished to a greater extent than normally by mere diffusion through the bronchial tubes, rather than by inflow and outflow of air. Under such conditions of retarded exchange one could not expect the oxygen tension in the alveoli to be kept as near as normal to the tension in the external atmosphere. Haldane, Meakins, and Priestley have found that "shallow breathing causes uneven ventilation of the lungs and this in turn produces anoxæmia." Meakins (a, b, and c) explains the cyanosis of pneumonia as due to such shallow breathing.

The second cause mentioned for the condition indicated in figure 13, viz., decreased permeability of the alveoli due to physical conditions

(presence of fluid, thickening of alveolar walls), is as yet a purely hypothetical possibility. It has been suggested, however, as a cause for the cyanosis, or susceptibility to cyanosis on slight exertion, observed in bronchopneumonia (Hoover), and in war gas poisoning (Barcroft, Hunt, and Dufton). Lately, Brauer has introduced the term pneumonosis to indicate a decreased permeability of the alveolar epithelium. In this way he explains the cyanosis which he observed in influenza patients before any anatomical lesions of the lungs could be detected. Marie Krogh introduced a method for the determination of diffusion constants, and obtained normal results in 4 patients with emphysema or with asthma, 1 with tuberculosis, and 3 with pneumonia. Whether a pathologically lowered diffusion constant for the alveolar membranes ever actually occurs is therefore not yet directly shown.

Another, but purely theoretical, possibility is that the blood can go so fast through the lungs (exercise, lung impairment) that an appreciable decrease in the normal saturation of the arterial blood results. The few experiments hitherto published on this subject show that a slight decrease in arterial oxygen saturation (about 1 to 2 volumes per cent), may take place during very strenuous exercise (Barcroft, Harrop). However, we do not know whether this is caused by difficulty in keeping up the alveolar oxygen tension, by increased acidity of the blood, or by the rapid blood flow itself.[6]

Figure 14 represents a condition in which part of the blood in the passage from the right heart to the arteries traverses a path to which access of air is anatomically impossible. Such a condition is observed in patients with congenital perforate septum of the heart, where a fraction of the blood is shunted directly from the right heart to the left, without passing through the lungs. It also occurs when anatomical obstruction prevents access of inspired air to any part of the lungs through which blood continues to flow.

Presumably the reason why one entire lung may be collapsed by pneumothorax or by pleuritic exudate, or almost filled with exudate in pneumonia, without occurrence of cyanosis, is that less than the normal half of the blood flows through the unaerated lung in these conditions;

[6] In a yet unpublished study Barr and Himwich have found a slight increase in the oxygen saturation of the arterial blood during and shortly after heavy exercise in man (personal communication added to proof).

and as will be shown later, about one-third of the blood may be shunted through an unaerated path from the right heart to the arteries before sufficient unsaturation results to cause cyanosis. In cases of exudative pleurisy and of pneumothorax in which an entire lung is compressed so as to prevent aeration, it appears probable that the pressure in

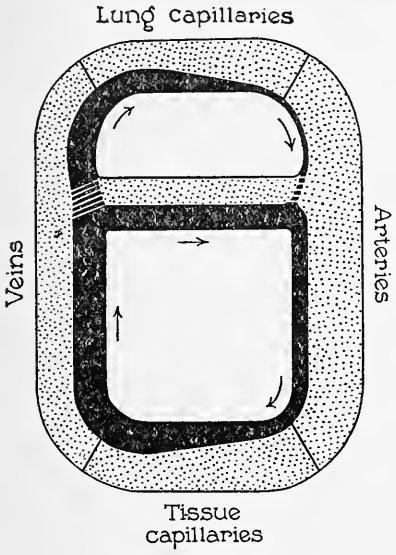

Fig. 14

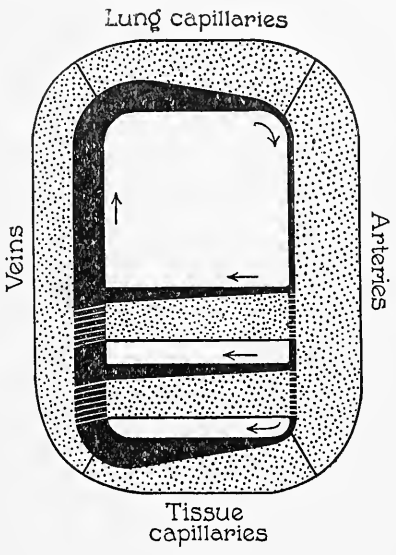

Fig. 15

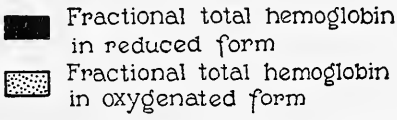

FIG. 14. DIAGRAM SHOWING THE PROPORTION OF OXYHEMOGLOBIN TO REDUCED HEMOGLOBIN IN DIFFERENT PARTS OF THE CIRCULATORY SYSTEM IN A CASE WHERE A FRACTION OF BLOOD PASSES THROUGH UNAERATED CHANNELS FROM VENOUS TO ARTERIAL SYSTEM

FIG. 15. DIAGRAM SHOWING THE PROPORTION OF OXYHEMOGLOBIN TO REDUCED HEMOGLOBIN IN DIFFERENT PARTS OF THE CIRCULATORY SYSTEM IN A CASE WHERE DEOXIDATION IS ABNORMALLY HIGH IN A PART OF THE PERIPHERAL CAPILLARIES AND NORMAL IN OTHER PARTS

the pleural sac exceeds that in the pulmonary artery, so that circulation from the latter is entirely cut off. In a patient with total compression of one lung from a large pleuritic exudate, Lundsgaard and

Möller (b) found that the cutaneous blood was 96 per cent saturated with oxygen, indicating that the compression of the lung had been so complete that not only aeration but also circulation had been prevented.

In pneumonia, conditions governing the blood flow through consolidated parts are variable. In typical lobar pneumonia when gray hepatization occurs the parts are almost bloodless. Patients of this type show much less tendency to become cyanotic than those with the type of bronchopneumonia frequently encountered in influenza, in which the lungs on section are found red and full of blood. Bronchopneumonia in children is also a condition where cyanosis is frequent, and in which the lungs are full of blood.

Although the result, deficient oxygenation of the arterial blood, is the same whether caused by incomplete alveolar oxygenation (fig. 13) or by an unaerated shunt of venous blood into arterial (fig. 14), yet it is of some importance to distinguish between the two causes. Differentiation between them may be difficult or even impossible in many cases. It may, however, influence both diagnosis and therapy.

In a case of retarded alveolar oxygenation (fig. 13), respiration of air with an increased oxygen concentration would increase the alveolar oxygen pressure and thereby the diffusion rate, with a resultant increase in the oxygen content of the arterial blood. Hence the efficacy of the oxygen treatment in mountain sickness, in gas poisoning, and in pneumonia (Haldane, 1917; Means and Barach, 1921; Barach and Woodwell, 1921; and Stadie, 1922).

In an unaerated shunt, on the other hand, with access of air completely prevented by anatomical obstruction, it is obvious that increase in oxygen tension of the inspired air could cause no oxygen absorption. In a case with such a shunt oxygen administration would only increase slightly the already nearly maximal oxygen content of the fraction of blood passing through aerated lung areas. The main cause of arterial unsaturation, venous blood shunted through an unaerated channel, would be unaffected.

It is a fact that may at first glance appear curious, that while an unaerated shunt prevents complete oxygenation of the arterial blood, the CO_2 tension and the pH of the blood may nevertheless be kept within normal limits. As pointed out by Haldane, Meakins,

and Priestley, by very rapid ventilation of the aerated lung areas the blood passing through them may have its CO_2 content so greatly reduced that when it rejoins the blood from the unaerated parts the mixture has the CO_2 tension and content of normal arterial blood. Hyperventilation of part of the blood can compensate, in CO_2 excretion, for entire lack of ventilation of the remainder; but because of the blood's limited oxygen capacity, it cannot compensate for entire lack of oxygenation in any considerable part of the stream.

We have above sharply differentiated between deficient pulmonary oxygenation (due usually to low alveolar oxygen tension) and the passage of venous blood into arterial through entirely unaerated channels, as causes of reduced hemoglobin in the arterial blood; and such sharp differentiation appears of assistance in classifying the causes of cyanosis and in calculating their relative influences on it. It is probable, however, that intermediate conditions exist, in which parts of the lungs although not absolutely separated by anatomical obstructions from the well aerated parts, are rendered so difficult to access by air that what one might term a functional shunt exists. The diffusion of air into such parts might be so slow and the oxygen tension reduced so nearly to that of venous blood that the effect would more or less closely approach that of complete separation from inspired air. Inspiration of air enriched with oxygen might raise the arterial oxygen content to more nearly normal than it would in a person with a completely unaerated shunt between veins and arteries, but not restore it entirely to normal. It is quite possible that such partially unaerated shunts occur in pneumonia, due either to partial bronchial obstruction or to the very shallow breathing.

Figure 15 represents the results of increased reduction of the oxygen during flow through the tissue capillaries. This would be caused either by decreased rate of flow through the capillaries, or by increased rate of oxygen consumption by the tissues. Decreased rate of capillary flow as a sole cause of cyanosis has been experimentally demonstrated only as a local condition. Cyanosis is a familiar occurrence when stasis is caused by ligating an extremity, and thereby retarding the capillary flow by venous back pressure. Lundsgaard (c) found that in a normal individual with a ligated arm, cyanosis began to appear in the arm and hand when the venous oxygen unsaturation

reached 10.2 volumes per cent. If we assume 1 volume per cent of arterial unsaturation, the mean capillary unsaturation was $C = \frac{10.2 + 1.0}{2} = 5.6$ volumes per cent.

In the local cyanosis caused by chilling the arm, Meakins and Davies found that when an arm became faintly bluish the unsaturation of the venous blood rose to 65.1 per cent of total capacity (which was 17.48 volumes per cent). The venous unsaturation was therefore $0.651 \times 17.48 = 11.4$ volumes per cent. The arterial was 0.7. The mean capillary unsaturation was, therefore, $C = \frac{11.4 + 0.7}{2} = 6.05$ volumes per cent, which is at the lower limit of the range (6 to 7 volumes per cent) of capillary unsaturation which Lundsgaard found to be usually associated with cyanosis. A very blue color was observed when the venous blood was entirely reduced, and $C = \frac{17.5 + 0.7}{2} = 9.1$ volumes per cent.

Another, theoretically possible, cause of retarded capillary flow and consequently increased capillary and venous unsaturation is a decreased minute output of the heart. That capillary flow may be so retarded by this cause that the latter by itself produces cyanosis, has not yet been definitely demonstrated. It probably is a contributing cause. Direct and indirect evidence has been obtained by several investigators that the resting minute volume of the heart is lowered in cardiac decompensation (Stewart; Hewlett; Means and Newburgh; Lundsgaard, a and b). Whether such retardation, by itself alone, is sufficient to raise the mean capillary unsaturation above the threshold for cyanosis is, however, uncertain. That many decompensated cardiac patients are cyanotic is certain. Lundsgaard and Möller (a) have suggested that patients with impaired heart function and decreased minute volume might be able to compensate to a certain degree for lack of reserve power of the myocardium by an abnormal distribution of the blood flow (through increased action of the vasomotor mechanism), providing in this way sufficient perfusion in some organs at the cost of the local blood flow in other organs. In this way the local results of a diminished minute volume of the heart

might be magnified in some regions, and local cyanosis possibly occur, partly as direct, partly as an indirect result of the decreased outflow from the heart.

QUANTITATIVE INFLUENCES OF THE DIFFERENT FACTORS CONTRIBUTORY TO THE PRESENCE OF REDUCED HEMOGLOBIN IN THE CAPILLARY BLOOD

The degree of cyanotic color developed by a given concentration of reduced hemoglobin is influenced by modifying factors, previously discussed, such as skin pigmentation and vascularity, which at present are not capable of quantitative consideration. Their variability must be allowed for by attributing a wide range, probably at least from 5 to 8 volumes per cent, to the threshold of mean capillary oxygen saturation at which cyanosis becomes evident. While the factors *modifying* the cyanotic color can be handled only by thus allowing for their variability, the factor *causing* the color, viz., the concentration of reduced hemoglobin in the skin capillaries, represents the summation of certain definite contributory factors which are to some degree susceptible of quantitative measurement or calculation. Reduced hemoglobin in the venous and arterial blood, and hence in the capillary, results primarily from two respective causes, oxygen consumption in the tissues and incomplete reoxygenation in the lungs. The magnitude of the effect of each may be influenced by a secondary factor.

The total hemoglobin content is such a factor. If reoxygenation in the lungs leaves a given fraction of hemoglobin in the reduced form (as is the case with a given lowered alveolar oxygen tension, for example), it is obvious that the resulting concentration of reduced hemoglobin is proportional to the total content of hemoglobin present, since it is a definite fraction of the latter. Consequently, the effect of deficient pulmonary ventilation on the content of reduced hemoglobin in arterial blood is proportional to the total hemogobin content, which is therefore an influencing, secondary factor.

The effect of oxygen consumption in the tissues is similarly influenced by a secondary factor, the fraction of blood traversing an unaerated shunt from right heart to arteries. Such a shunt pours some of the venous blood directly into the arterial. Consequently, deoxygenation in the tissues causes not only venous unsaturation but

also some arterial unsaturation. Thereby the effect of tissue deoxygenation on the capillary unsaturation is augmented beyond what it would be if all the hemoglobin were reoxygenated before reaching the arteries. In this case, deoxygenation of blood in the tissue capillaries increases not only V but also A, which together determine the mean capillary unsaturation $\left(C = \frac{V + A}{2}\right)$.

There may therefore be four factors involved in increasing the capillary content of reduced hemoglobin, viz.: (1) deficient pulmonary oxygenation, the effect of which is proportional to (2) the total hemoglobin content, and (3) during passage of the tissues, increased oxygen consumption, the effect of which may be augmented by (4) the presence of an unaerated channel through which venous blood reaches the arteries.

The quantitative effects of these four factors are indicated by a formula developed as follows:

Let

T = total hemoglobin content of the blood.

A = reduced hemoglobin content of arterial blood.

V = reduced hemoglobin content of venous blood.

D = content of hemoglobin deoxygenated in passage of blood from arteries to veins ($D = V - A$).

l = fraction of total hemoglobin passing in reduced form through *aerated* portions of lungs.

α = fraction of total blood shunted through *unaerated* channels from right heart to arteries.

C = mean reduced hemoglobin content of capillary blood.

The mean reduced hemoglobin content of the capillary blood is expressed as explained before by the equation

$$C = \frac{A + V}{2} \tag{1}$$

When there is no unaerated shunt, and $\alpha = 0$, we have the relationship

$$A = lT \tag{2}$$

This simply expresses the fact that since all the arterial blood passes through aerated parts of the lungs in going from the right heart to the

left, the content, A, of reduced hemoglobin in the arterial blood is equal to lT, the product of the total hemoglobin content, T, multiplied by the fraction of hemoglobin, l, still in the reduced form on entering the arteries.

However, when a certain proportion, α, of the blood, is shunted through a perforate septum in the heart, or through unaerated portions of the lungs, A exceeds lT, because a fraction, α, of blood with the higher reduced hemoglobin content, V, of venous blood, is mixed with $1 - \alpha$ part of aerated pulmonary blood, with lT content, to form the arterial blood, with reduced hemoglobin content A between lT and V. The exact relationships in such a case are indicated by equation (3).

$$A = (1 - \alpha)\, lT + \alpha V \tag{3}$$

If (3) is solved for α, we obtain:

$$\alpha = \frac{A - l\,T}{V - l\,T} \tag{4}$$

This is an expression which may be of use in estimating the value of α experimentally.

To express α in terms of V and D, instead of V and A, we substitute $V - D$ for A in (4) and obtain

$$\alpha = \frac{V - D - l\,T}{V - l\,T} \tag{5}$$

Solving (5) for V we obtain

$$V = l\,T + \frac{D}{1 - \alpha} \tag{6}$$

Similarly, we substitute $A + D$ for V in (4) and obtain

$$\alpha = \frac{A - l\,T}{A + D - l\,T} \tag{7}$$

Solving (7) for A we obtain

$$A = l\,T + \frac{\alpha\, D}{1 - \alpha} \tag{8}$$

We now substitute for A and V in equation (1) their values as expressed in (6) and (8), and thereby obtain (9), which shows the quantitative effects on C of all four factors considered.

$$C = l\,T + \frac{(1 + \alpha)\, D}{2\,(1 - \alpha)} \tag{9}$$

Equation (9) also indicates the manner in which, as stated before in words, T influences the effect of l, and α the effect of D on C.

SEPARATE EFFECTS OF THE INDIVIDUAL FACTORS CONTRIBUTING TO THE REDUCED HEMOGLOBIN OF THE CAPILLARY BLOOD

In order to illustrate the effect of each of the four factors we have calculated C, assuming in turn that one factor at a time undergoes the extreme possible variations while the others remain normal. Expressing reduced hemoglobin concentration in terms of volumes per cent of oxygen unsaturation, and hemoglobin content, T, also in oxygen terms as total oxygen capacity, we have taken as the normal figures, $T = 20$, $D = 5$, $l = 0.05$, $\alpha = 0$.[7] If we keep T, D, and l at these values, permit α to vary from zero towards 1, and calculate the corresponding C values, we obtain the curve on figure 16 marked α. In a similar way the curves l, D, and T are obtained.

For l, D, and T the ordinary ranges of the values for a normal resting adult (D may normally be increased by exertion) are indicated by brackets on their respective curves (α normally is zero).

It becomes obvious from a glance at figure 16 that the factor which, in proportion to its deflection from the normal, has the greatest effect in producing capillary oxygen unsaturation, is l.

When this fraction reaches 0.2, *the other factors remaining normal*, the mean capillary oxygen unsaturation reaches 6.5 volumes per cent, at which cyanosis usually appears. As a matter of fact, Barcroft and his party in the Andes (1922) found that cyanosis did appear when the oxygen unsaturation of arterial blood reached 15 to 20 per cent of the total capacity. Binger, Hastings, and Neill found cyanosis appearing in a pneumonia patient also at about this range of arterial oxygen unsaturation. The absence of an unaerated shunt in this patient was demonstrated by the fact that doubling the oxygen tension in the inspired air raised the arterial oxygen saturation to normal.

[7] Values for T, A, V, D, and C, can all be expressed in volumes per cent (see footnote 4). That T is 20 volumes per cent, means that hemoglobin is present in the blood in such a concentration (15 grams per 100 c. c. of blood) that 20 c. c. of oxygen can combine chemically with 100 c. c. of blood. A value for D of 5 volumes per cent, means that 5 c. c. of oxygen per 100 c. c. of blood has been taken away from the blood during its passage through the tissue capillaries. l and α are expressed simply as fractions of T and of the total blood flow per minute, respectively. A value of 0.05 for l means that the oxygenation of the blood in the aerated part of the lungs is 95 per cent of its maximal value. That α is 0.3 means that 30 per cent of the blood going to the right side of the heart passes through an unaerated channel to the left side.

The factor of second importance, regarded from the proportion of its maximum extent that must be reached to cause cyanosis, is α, the fraction of blood passing through unaerated channels from right

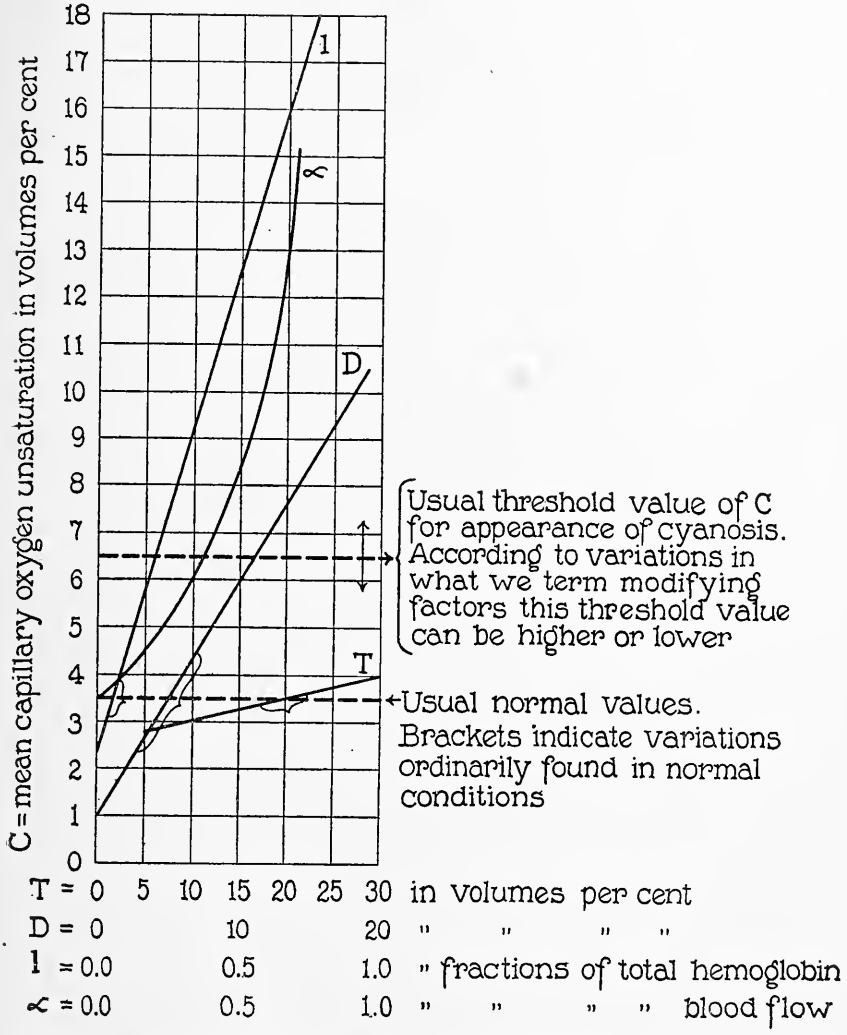

FIG. 16. DIAGRAM SHOWING THE RELATIVE MAGNITUDE OF THE INFLUENCE ON MEAN CAPILLARY OXYGEN UNSATURATION (C) OF VARIATIONS IN TOTAL OXYGEN COMBINING POWER OF THE BLOOD (T), IN DEOXIDATION RATE DURING THE PASSAGE OF BLOOD THROUGH THE CAPILLARIES (D), IN THE FRACTION OF TOTAL HEMOGLOBIN PASSING UNOXIDIZED THROUGH AERATED PARTS OF THE LUNGS (l), AND IN FRACTION OF BLOOD (α) PASSING FROM RIGHT TO LEFT THROUGH CHANNELS TO WHICH AIR HAS NO ACCESS

heart to arteries. From figure 16 it is evident that, other factors remaining normal, α may become as great as one-third of the total blood stream before what may be termed the cyanotic threshold is crossed. That so much venous blood could be mixed with arterial before cyanosis appears was not recognized by past investigators of cyanosis, and in consequence there arose much confusion in the field, the occurrence of any unaerated shunt at all without cyanosis being accepted by some as proof against such a shunt as a possible cause (see historical discussion, page 64).

The third factor in its relative isolated influence on the capillary mean content of reduced hemoglobin is D, expressed as volumes per cent of oxygen taken from the blood in its passage from arteries to veins. D is normally about 5 volumes per cent. Its theoretical maximum with 20 volumes per cent total oxygen capacity, 1 volume per cent arterial unsaturation, is of course 19. And with the other factors all normal, it can rise to about 12, or over 0.6 of this, before C crosses the cyanotic threshold. It becomes comprehensible, why, in normal individuals, the venous oxygen may fall unusually low without the occurrence of cyanosis.

It is obvious from figure 16 that changes in the fourth factor, T, the total hemoglobin content, have relatively slight effect on the capillary reduced hemoglobin content. As pointed out before, however, (page 27) the total hemoglobin content does determine the effect on C of deficient pulmonary oxygenation (high value of l). Similarly, the value of D, through its influences on V, determines the effect of α on C. The quantitative nature of the effect on C of combinations of l, T, D, and α, respectively, forms the subject of the next paragraphs.[8]

[8] The effects on C of separate variations of l, T, D, and α, shown graphically by the curves of figure 16, are shown in a more general way by partial differentiation of equation (9) with respect to each factor in turn. Thus we obtain:

$$\delta C = T \delta l \tag{10}$$

$$\delta C = l \delta T \tag{11}$$

$$\delta C = \frac{D}{(1 - \alpha)^2} \delta \alpha \tag{12}$$

$$\delta C = \frac{1 + \alpha}{2 (1 - \alpha)} \delta D \tag{13}$$

(10) and (11) bring out the effect of T on the result of l changes, and vice versa, while (12) and (13) do the same for α and D.

COMBINED EFFECTS OF THE FACTORS CONTRIBUTING TO THE PRESENCE OF REDUCED HEMOGLOBIN OF THE CAPILLARY BLOOD

As pointed out in the previous pages from a consideration of the physiological relations, a given degree of deficiency (l) in oxygenation of the pulmonary blood produces an amount of reduced hemoglobin proportional to the total hemoglobin present (T). And the further amount of reduced hemoglobin in the circulation produced by a given consumption in the tissues (D) is magnified by the pouring of a part (α) of the deoxygenated venous blood through an unaerated channel into the arteries. The total reduced hemoglobin produced is the sum of that due to l and T acting together (this amount being represented in equation (9) by the term lT), plus that due to D and α acting together $\left(\text{represented by the term } \frac{(1 + \alpha)\ D}{2\ (1 - \alpha)}\right)$. While, therefore, we would be correct in merely adding the separately calculated effects on C of given increases in l and D, we could not, when l and T both vary, calculate separately the effects of given increases in each, such as might be estimated by interpolations on the l and T curve of figure 16, and by adding the increases there found, correctly estimate the resultant C. A given increase in T augments the effect of a given increase in l and vice versa; and α and D are likewise related. Consequently, for a view of the influences of the factors when more than one at a time is abnormal it is necessary to consider them not singly, but in pairs, l and T being treated together because of their mutual influence on each other, and likewise D and α.

A. Combined effect of simultaneous variations in pulmonary oxygenation (l) and in hemoglobin content (T)

We have expressed in figure 17 the volumes per cent of capillary oxygen unsaturation produced by variations in l and T together, calculated as $C = lT$. In figure 17 we have indicated also the total C that would result from the effect of these factors added to the effect of a normal D of 5 with $\alpha = 0$. It is obvious that the reduced hemoglobin content, C, in the capillaries produced by passage through the lungs of a given hemoglobin fraction l in the reduced form is dependent on the total hemoglobin content T. The values of l which pro-

duce the capillary unsaturation usually necessary for cyanosis to become apparent, viz., 6.5 volumes per cent, are, from figure 17, the following:

T HEMOGLOBIN CONTENT	l TO PRODUCE $C = 6.5$ FRACTION OF HEMOGLOBIN PASSING LUNGS IN REDUCED FORM
volume per cent oxygen capacity	
5	Impossible for C to be as great as 6.5
10	0.40
20	0.20
30	0.15

From the above table it is evident that a person with only 25 per cent of normal hemoglobin ($T = 5$) can ordinarily not become cyanotic, and one with 50 per cent becomes cyanotic from deficient pulmonary oxygenation only when the deficiency is so great as to permit about 40 per cent of the hemoglobin to pass the lungs unoxidized. A polycythemic person, on the other hand, with $T = 30$, would pass the usual cyanotic threshold, $C = 6.5$, when the blood left his lungs with only 15 per cent of its hemoglobin unoxygenated.

The nature of the combined effects of deficient pulmonary oxygenation and blood hemoglobin concentration on the production of cyanosis appears hitherto to have escaped notice, with some resulting confusion in the interpretation of clinical observations. The reason for the readiness of polycythemic patients to become cyanotic has not been understood, and polycythemia in itself has been considered as a cause of cyanosis. As illustrated by figure 17, polycythemia can markedly enhance the cyanotic effect of deficiency in oxygenation.

It is evident, therefore, that the presence and extent of deficient pulmonary oxygenation cannot be judged with any degree of accuracy from the skin color produced unless the other factors, D, α, and T, but especially the hemoglobin content, T, are taken into consideration.

Another point of interest in this connection is that a person who becomes polycythemic because of the well known physiological increase in hemoglobin at high altitudes, might show a cyanosis in the rarefied atmosphere, while cyanosis might not be evident in a normal or anemic person with the same fraction of reduced hemoglobin in his arterial blood. In this case the cyanotic individual would be the one in better physiological condition.

The influence of venesection in clearing up cyanosis is doubtless due to some extent to the lowering of the hemoglobin content, although the main factors are probably reduction in D due to improved circula-

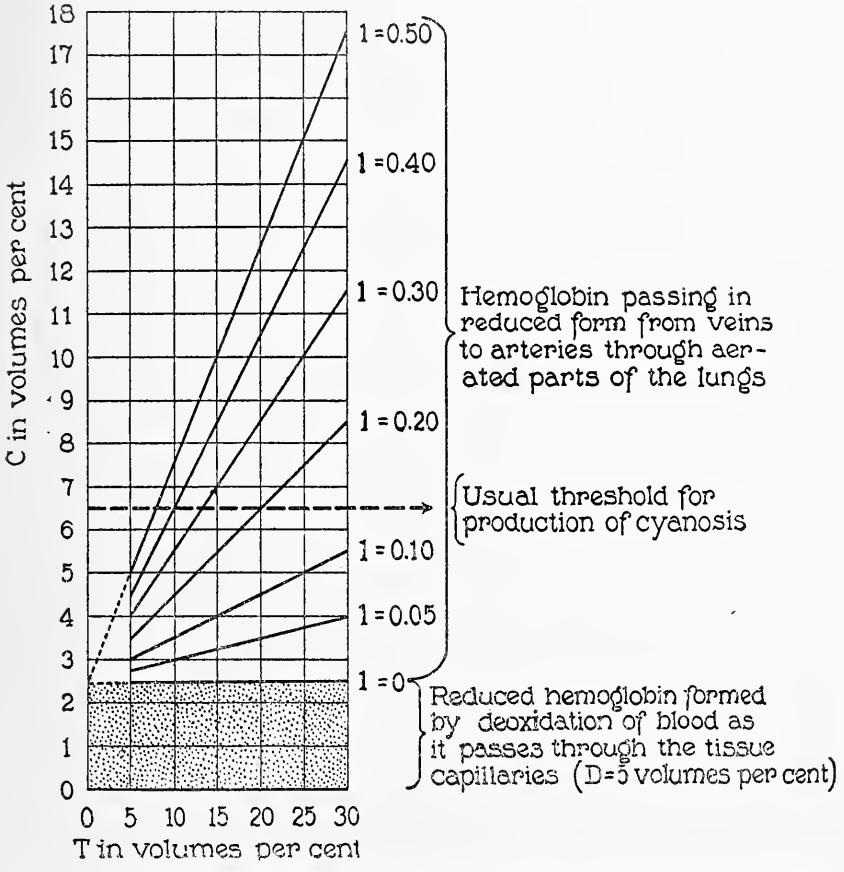

FIG. 17. DIAGRAM SHOWING INFLUENCE ON THE MEAN CAPILLARY OXYGEN UNSATURATION (C) OF SIMULTANEOUS VARIATIONS IN T AND l

tion and in l due to relief of pulmonary stasis. This procedure may, by relieving peripheral stasis, also diminish the effect of one of the modifying factors, the distension of the capillaries.

B. Combined effect on C of simultaneous variations of the oxygen consumption (D) and the fraction of blood shunted (α)

The influence of D on the capillary unsaturation is in most instances mainly local on account of the great variations of blood flow in the

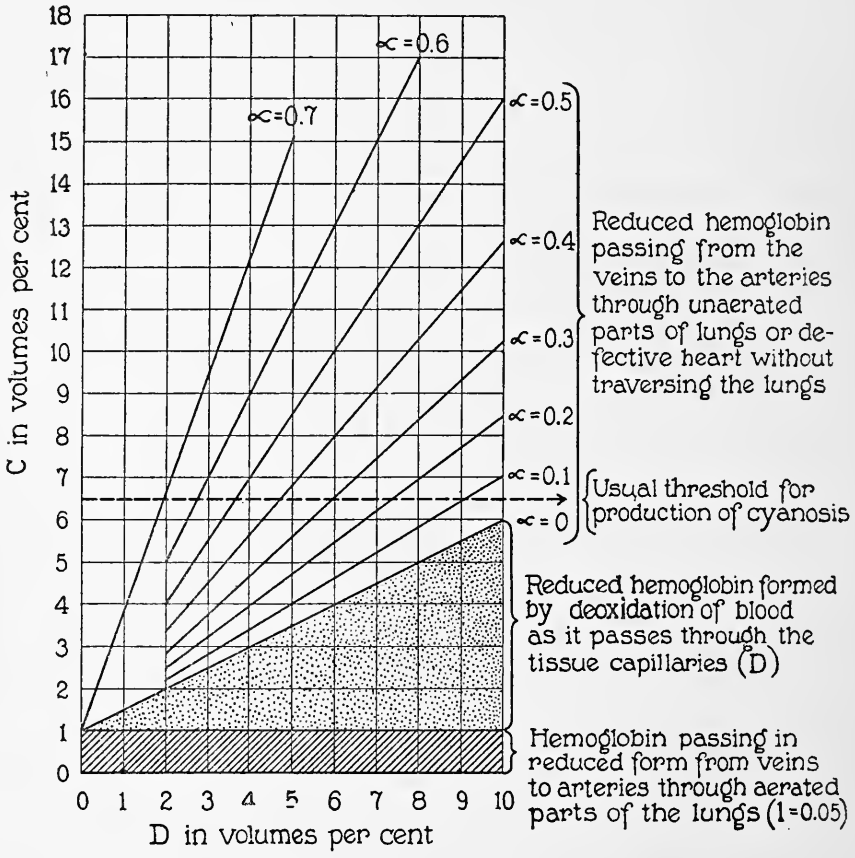

FIG. 18. DIAGRAM SHOWING INFLUENCE ON THE MEAN CAPILLARY OXYGEN UNSATURATION (C) OF SIMULTANEOUS VARIATIONS IN D AND α

different regions of the body. (See, for example, the local effect of cooling the arm observed by Meakins and Davies.) If, however, a shunt is present and a certain fraction of the venous blood passes unaerated into the arterial stream, the unsaturation of the combined

venous blood in the right heart, resulting from the average D value of the entire capillary system, exerts an influence on the arterial unsaturation and thereby on C. With constant metabolism, the average D is inversely proportional to the minute volume output of the heart. In exercise, as previously mentioned, the blood flow does not increase in the same proportion as the oxygen consumption, so that D normally increases with local functional activity. The effect of simultaneous variations in α and D on C is shown in figure 18, in the same manner that the effects of l and T were shown in figure 17.

From figure 18 it is evident that, with normal pulmonary oxygenation ($l=0.05$) and normal hemoglobin content, the variability with varying α indicated in the following table exists in respect to the size of D required to raise C to the usual cyanotic threshold.

α	CAPILLARY OXYGEN CONSUMPTION, D, RESULTING IN C OF 6.5 VOLUMES PER CENT
	volume per cent oxygen
0.0	11.0
0.1	9.0
0.2	7.4
0.3	6.0
0.4	4.8
0.5	3.7
0.6	2.8
0.7	2.0

The influence of α in magnifying the effect of D on C is one of the reasons for the readiness with which cyanosis develops or increases, during exercise, in a patient with an unaerated shunt.

Since D depends on the ratio of blood flow rate to oxygen consumption rate in the capillaries, retarded circulation would have the same effect as increased oxygen consumption (exercise) in increasing D. If this effect is magnified by the presence of an unaerated channel admitting venous blood into the arterial, a slight retardation of the minute output of the heart (slight decompensation) might cause cyanosis in a patient with an unaerated shunt, whereas no cyanosis would ensue in an individual without a shunt.

It is further evident that if α is great enough ($\alpha = 0.38$), even the usual oxygen consumption ($D = 5$) causes a C exceeding the usual

cyanotic threshold of 6.5 volumes per cent unsaturation. Hence there occurs the intense cyanosis observed in children with congenital perforate septum and right to left shunt. In such cases there is usually also a polycythemia, so that the lT effect discussed above is added to the αD effect.

Finally, it is to be noted that since, with other factors normal, about 38 per cent of the venous blood must be shunted through an unaerated channel into the arteries before the cyanotic threshold of C is reached, if by a more rapid circulation D is lowered, α may be still higher without causing a C above the threshold. Consequently, absence of cyanosis in a resting patient does not exclude the possibility that a large fraction of his blood is passing through parts of the lungs to which no oxygen has access, or through other unaerated channels from the venous to the arterial system.

In the above consideration of the combined effects of D and α, D is considered to be the mean difference between arterial and venous oxygen contents, as expressed by the bloods in the arteries and right heart. Locally increased D values would, as shown in figure 15, affect the average unsaturation of the total blood, and C, only to the extent that they increase the reduced hemoglobin content of the combined venous bloods in the right heart.

If therapeutic means are applied which may simultaneously affect more than one of the three factors, l, T, and D, that çan be varied in a given case (α being presumably constant in an individual over a short period of time), and cyanosis disappears or diminishes, it may not be possible to draw conclusions as to the main, original cause of the cyanosis. If oxygen therapy alone causes its disappearance, the main cause may be assumed to have been inefficient oxygenation in the lungs (high l). If digitalis causes the color to become normal, the cause of cyanosis may have been either retarded circulatory rate (high D value), or it may have been pulmonary embarrassment (high l value), since, as before mentioned, decompensated cardiacs show decreased lung volumes and oxygenation may be deficient. If venesection (lowering the hemoglobin content, T) or oxygen therapy (lowering l) is used together with digitalis, the interpretation of a disappearance of cyanosis is still more uncertain.

CLINICAL CONDITIONS ASSOCIATED WITH CYANOSIS

We shall in the following pages discuss the available data, indicating which factors are active in the production of cyanosis in the more important diseases in which it is encountered. Our present knowledge is so incomplete in most cases that it is only of suggestive value. There are a few conditions, however, in which the blood oxygen has been sufficiently studied, or the clinical condition so carefully analyzed, or both procedures have been so combined, as to indicate at least the probability concerning which of the contributory factors are responsible for the cyanosis. And perhaps discussion of conditions in which there is no satisfactory information may be of value in indicating problems that are urgently awaiting solution by exact study.

A. Diseases of the lungs and the air passages

A. Tracheal and bronchial stenosis. In patients suffering from stenosis of the trachea (foreign bodies, edema of the glottis, croup, etc.) cyanosis is a common and usually extremely marked symptom. No analyses of blood are available in such cases. The whole acute nature and dangerous character of these conditions makes it unlikely that such information can be easily obtained. It is, however, clear that decreased oxidation in the lung (increased l) is mainly, if not exclusively, responsible for the cyanosis in these cases. No other factor is likely to be involved in the production of the increased unsaturation of the capillary blood. Similarly, any large abnormality in the state of the modifying factors may be excluded. In these cases carbon dioxide retention adds its effect to that of anoxemia in causing the distress of the patient and producing the symptoms of suffocation.

In cases of bronchial stenosis cyanosis is not always observed. The acting factor here is a positive α, part of the lung being unaerated, although blood (α part of the whole) still flows through it. As we have estimated above, the value of the fraction α may reach about one-third before cyanosis appears. This means that about two-thirds of one lung may be shut off from aeration without appreciable cyanosis if l, T, and D are unchanged and the modifying factors normal. Oxygen therapy cannot relieve patients with tracheal and bronchial stenosis if the obstruction is total.

A series of experiments by Loewy and von Schrötter on the minute volume in man is interesting in this respect. By blocking a bronchus they cut a certain part of the lung off from aeration while the circulation was not hampered. They found that in normal individuals two-thirds of one lung (the right upper and middle lobe of the right lung) could be shut off from aeration without occurrence of cyanosis. When one whole lung was cut off cyanosis ensued. Some of their experiments lasted more than half an hour.

Table showing determinations of arterial oxygen unsaturation before and after obstruction of the air passage to one lung in animals (after Le Blanc)

SPECIES	OXYGEN CONTENT OF ARTERIAL BLOOD IN VOLUMES PER CENT		α ESTIMATED VALUE* OF FRACTION OF BLOOD PASSING LUNG TO WHICH AIR HAS HAD NO ACCESS
	Before obstruction of main bronchus to one lung	After obstruction of bronchus	
Rabbit	13.63	9.81	0.43
Rabbit	14.55	8.70	0.54
Rabbit	13.33	8.88	0.47
Rabbit	13.18	7.66	0.52
Rabbit	10.42	7.66	0.36
Cat	16.25	12.41	0.43
Cat	15.94	11.18	0.49
Dog	17.16	10.73	0.56
Goat	13.99	10.42	0.41

* Calculated by us from equation (4) (page 29) under the assumption that $D = 5$ volumes per cent and $l = 0.05$.

Our calculation that, with other factors normal, about one-third of the venous blood ordinarily must be shunted without aeration into the arteries in order to produce cyanosis, is in conformity with the results of these experiments, if we can assume that the normal fraction of blood passes through a part of the lung made inaccessible to aeration by bronchial obstruction. Hess (1912) and Le Blanc (1922) showed this to be the case in animals observed under similar conditions. Hess found that bronchial obstruction in rabbits had the calculated effect on arterial oxygen unsaturation, if the calculation was based on the assumption that the normal fraction of blood passed the lung after bronchial obstruction. Le Blanc, in 1922, obtained the results

tabulated above, and drew from his experiment the conclusion that obstruction of a bronchus does not markedly change the proportion of blood flowing through the right and left lung, respectively. We have, by applying our equation (4) for the calculation of α, and by assuming normal figures for D and l, estimated the fraction of blood passing the lung excluded from aeration. The figures show that from 36 to 56 per cent of the blood has traversed the obstructed side. No statements were made as to the side on which the operation was performed. The experiments, therefore, give no information regarding a possible difference in blood flow between the right and left lung.

B. Bronchitis. Bronchitis in adults is as a rule associated with cyanosis only if it is combined with other diseases such as emphysema and heart disease. Bronchitis may, as mentioned under the description of these conditions, then be an assisting factor in raising the capillary oxygen unsaturation to a point great enough to cause cyanosis. Bronchitis in children and babies is often associated with marked cyanosis. This may be due to the fact that the bronchitis in such cases usually is a bronchiolitis obstructing the air passages, as indicated at the post-mortem examination by the presence of atelectases of the lung tissue. It is, therefore, justifiable to assume that in such cases an increased arterial unsaturation exists, caused by shunting of small fractions of blood through unaerated parts; or, so to speak, by the additive effect of several α's. Concerning the modifying factors nothing is known, but it seems fair to assume that they play a minor part.

C. Emphysema pulmonum. "Cyanosis of an extreme grade is more common in emphysema than in other affections with the exception of congenital heart-disease. It is one of the few diseases in which a patient may be able to go about and walk into the hospital or consulting-room with a lividity of startling intensity." (Osler and McCrae, 1920.) It is, furthermore, characteristic that cyanosis in emphysematic patients increases markedly in exercise. Our information about the respiratory and circulatory disturbances in emphysema is still so incomplete that an exact physiological explanation cannot be given. That incomplete pulmonary reoxygenation of the blood is mainly responsible for cyanosis, seems probable in view of the well established pathological condition of the lung volumes (Siebeck; Lundsgaard and

Schierbeck), and the common complication with bronchitis in these cases. No analyses of the arterial blood are at hand to elucidate this question. In one patient, Lundsgaard and Möller (1922) found that the cutaneous blood was 96 per cent saturated, but no cyanosis was present in this case. Whether a hypothetically decreased reoxygenation of the blood in the lungs is due to increased l or positive α we do not know. M. Krogh did not find any decreased diffusion in three cases of emphysema, but none of these cases was reported to be cyanotic. That increased D, on account of slow circulation, plays an important part in producing cyanosis in emphysema, except in cases with heart failure, seems unlikely. Of the modifying factors little is known. It is a clinical experience that the superficial veins often are distended, especially in advanced cases (increased venous pressure?). To what extent this increases the width and the number of the blood-filled capillaries is not known.

D. Asthma bronchiale. Attacks of bronchial asthma are usually associated with a marked degree of cyanosis. The physiological pathology of this condition is unknown. However, clinical observations and what little we know about the changes of the lung functions (increased residual air, decreased vital capacity, prolonged and difficult expiration) point to incomplete pulmonary oxygenation (increased l) as the main factor involved. Direct evidence from oxygen analyses of arterial blood is still lacking. Increased D is probably seldom a significant factor. Distension of the veins, which is often seen during the attacks, may increase the importance of one of the modifying factors (the capillary distension). In asthma, as well as in emphysema, a diffuse bronchitis may add its influence to the other factors. In many cases the secretion in the air tubes may perhaps even be the main factor in diminishing the oxygenation of the blood during its passage through the lungs.

E. Pneumonia. Cyanosis is an important symptom in pneumonia patients. It is usually ascribed to respiratory disturbances. The following will show that in the main this is justified. By some clinicians, however, it is still looked upon as indicative of circulatory failure and treated accordingly. In spite of a number of studies of the condition, including some in which observations have been made

on the blood gases, we are yet uncertain concerning the main factor in preventing the reoxygenation of the blood in the lungs.

Hürter analyzed, in 1912, the arterial blood in two cases of pneumonia. He found in one case a saturation of 85 per cent; in another case, 78.6 per cent unsaturation (respectively, 2.74 and 3.29 volumes per cent). In the first case the left and right lower lobes were involved; in the last case, the right lower lobe was affected, and possibly the middle and upper also. He did not state whether or not cyanosis was present. If we assume that l and D are both normal (0.05 and 5.0, respectively), and attribute the cyanosis entirely to a fraction of blood passing unaerated (consolidated) parts of the lungs, we calculate that in the first patient the fraction was 0.27, and in the second 0.33. That would mean that about one-third of the blood perfused the unaerated parts, which in the first case comprised about 0.4, and in the second, between 0.2 and 0.5 per cent of the total lung tissue. This proportion of the venous blood can, as previously shown, enter the arteries unaerated without causing cyanosis. However, as we shall indicate later, it is not probable that arterial oxygen unsaturation in pneumonic patients is exclusively or even mainly due to an anatomical shunt.

Stadie's analysis of the oxygen content of the arterial blood in 33 patients with influenzal pneumonia (including 6 of the lobar type) (1919), and in 8 patients with lobar pneumonia (1922), shows that insufficient oxygenation of the blood is the most important cause of cyanosis in this condition. Increase in the oxygen consumption, D, was not often observed. The average value of D in Stadie's cases (1919) was normal. Le Blanc examined the blood gases in 6 patients with lobar pneumonia, 2 of whom showed slight cyanosis. In 1 patient (no. 20) with a slight cyanosis of the lips, ears, nails, and mucous membranes, he found an arterial oxygen unsaturation of 2.78 volumes per cent and a venous unsaturation of 6.69 volumes per cent. Calculated from these figures, the mean capillary oxygen unsaturation would be 4.73 volumes per cent, or slightly below what was found by Lundsgaard as the usual lower level. In another patient (no. 24) acrocyanosis was present with an arterial unsaturation of 1.92 volumes per cent and a venous unsaturation of 4.53 volumes per cent,

which gives a mean capillary oxygen unsaturation of only 3.22 volumes per cent. It must be remembered, however, that venous blood drawn from the cubital vein may differ considerably from venous blood from the acrocyanotic region. It is not at all improbable that peripheral disturbances in the circulation are mainly responsible for cyanosis in this last case. So far, however, no studies have been undertaken to investigate the condition of the capillaries in such cases, and their relation to cyanosis. A certain tendency to icterus exists and this may interfere with the shade of the color produced. Whether or not the heliotrope coloration in these cases can be ascribed to a mixture of ordinary cyanotic color and icteric color, we do not know; but the fact that a heliotrope variation of the cyanotic color has so far not been reported in, for instance, cardiac patients with cyanosis, points against this conception. The possibility that the heliotrope color could be caused by the presence of methemoglobin can probably be excluded because neither Abrahams, Hallows, and French, nor Stadie (a) could find any evidence of methemoglobin in the blood in their cases.

Whereas it seems proved that the main source of cyanosis in pneumonia is insufficient oxygenation in the lungs, it is still uncertain whether this is to be attributed to an increased l, that is to an insufficient oxygenation of blood passing aerated lung tissue, or to a positive α, that is to a fraction of blood passing consolidated, unaerated lung tissue. Most facts, however, seem to point to the first explanation, namely, that an increased l is the main factor. The disappearance of cyanosis after oxygen administration in these cases (Means and Barach; Barach and Woodwell; and Stadie, b) is evidence against a positive α. Furthermore, the extensive consolidation found without cyanosis in Stadie's (b) cases, nos. 1, 2, and 6, and the dry, bloodless condition of the consolidated parts of the lung in the stage of gray hepatization make it appear that the blood flow through the affected part is either prevented or much diminished, so that it is not likely to approach the necessary fraction ($\alpha = \frac{1}{3}$) of the total blood flow required to cause cyanosis. Kline and Winternitz showed that by injecting the lungs of rabbits and of man with Berlin blue through the pulmonic artery, only a very scanty color was produced in the consolidated region, whereas the normal parts were deeply stained; and by means of x-ray examinations of human lungs injected with a

Fig. 19. X-Ray Photograph of Pneumonic Lung (Pneumonia Lobaris Lobi Super. et Med.) Injected with Barium Sulphate Gelatine through the Pulmonary Artery. The Upper Lobe Shows Fewer Vessels than Are Normally Found. In the Middle Lobe only the Largest Branches Are Injected. The Shadow of the Lower Lobe Is More Dense and Massive than Usual, Suggesting a Compensatory Dilatation of the Vessels in the Non-Consolidated Area (after Gross)

barium emulsion Gross found that the pulmonic vessels in the regions of gray hepatization were almost completely impassable for the injected matter (fig. 19). This obstruction to the blood flow in the stage of gray hepatization is usually ascribed to pressure from the intra-alveolar exudate. Kline and Winternitz, however, have found some evidence pointing, as they believe, to multiple capillary fibrinogenous plugs (thrombi) in the pneumonic vessels as the cause. It is in this respect interesting that it has been shown (H. C. Gram) that in influenzal pneumonia (at the height of the disease) a very marked decrease in the blood platelets occurs. In twelve patients examined by Gram, the average number of blood platelets was 174,000 instead of 400,000 normally present. The highest observed value was 308,000, the lowest 46,000. In several of the patients a tendency towards hemorrhage was present. It seems possible, therefore, that the reason why the circulation is not cut off in the affected region of the lungs in patients with influenzal pneumonia, might be due to a diminished tendency of the blood to clot on account of platelet deficiency. The question is of theoretical and practical importance in many respects and needs further investigation.

Stadie reports one case (no. 2) with consolidation of the entire lower lobe, and entirely normal arterial oxygen (95 per cent of complete saturation) without oxygen therapy. Similarly, Le Blanc finds normal arterial oxygen saturation (98.1 per cent) in a patient with gray hepatization of part of the left lower lobe. It is, therefore, probable that the cyanosis is at least not mainly due to a shunt of blood through consolidated parts of the lungs in pneumonia. Whether it is due to shallow breathing (as suggested by Meakins, a and b), or to layers of fluid in alveoli (Hoover), or to decreased diffusion due to toxic injury to the alveoli (pneumonosis, Brauer), not filled with solid or fluid matter, we cannot decide.

Cyanosis was found to be a much more common and marked symptom in pneumonia patients during the influenza epidemics than in ordinary lobar pneumonia. This may be explained in part by the fact that the anatomical processes in influenzal pneumonia are different from those in ordinary lobar, and are such as to permit a large blood flow through unventilated pulmonary tissue. Influenzal pneumonia is usually of the bronchopneumonic type. On section,

the cut surfaces of such lungs were found to be red in color, and very rich in blood. Although one cannot with certainty draw conclusions as to the rate of perfusion from the amount of blood in the lung tissue, the appearance at least indicates that the blood flow was not prevented in the affected parts, as it probably is more or less prevented in lobar pneumonia. Apparently, anatomical conditions in influenzal pneumonia favor the production of a positive α to a larger extent than do those in lobar pneumonia. On the other hand, clinical observations have been made (Brauer) of cyanosis in such patients at a very early stage of the disease, before any anatomical lung lesion could be detected. In such cases an increased l would presumably be present. These observations led Brauer, as previously mentioned, to introduce the term pneumonosis.

F. Edema of the lungs. The mechanism causing cyanosis in edema of the lungs in man is not known. It is, however, probable as suggested by Hoover, that the accumulation of fluid along the epithelial walls of the lungs decreases the diffusion constant of oxygen. The same explanation is given by Barcroft for cyanosis in war gas poisoning, where edema was frequently observed. Oxygen therapy has been applied with success in many cases of edema of the lungs. Schjerning has produced lung edema in cats and dogs by intravenous injection of chloramine and subcutaneous injection of urethane, and also by chlorine inhalation. He found incomplete oxygenation of the arterial blood in these cases. In 2 cases (dogs 9 and 13) the anatomical changes in the lungs after chlorine inhalation were so slight that he assumes a functional disturbance of the epithelium (pneumonosis) as the cause of the marked increase in the arterial oxygen unsaturation.

It is, therefore, justifiable to assume that the main factor in producing cyanosis in patients with lung edema is increased l and that oxygen therapy consequently has effect in such cases. In some gassed patients an increased T has been observed (Barcroft and his associates) which may augment the influence of l, as previously discussed. In cases of heart failure with lung edema, a slow circulation may, through increased D, add its effect to the increased l. As to the modifying factors nothing is known. In heart conditions a distension of the peripheral capillaries may be present. Otherwise, the modifying factors seem to play a small part.

G. Pneumothorax and pleural effusion (collapsed and compressed lung). Acute (open) pneumothorax is usually associated with cyanosis, which in such a case is produced in the same manner as when the air passages to one lung are blocked, viz., by blood flow through unaerated lung space (positive α). Experimental evidence for this has been given by Sackur, who produced collapse of one lung by open pneumothorax in 5 rabbits and 1 dog. He determined the oxygen content in the arterial blood before and after the operation, and obtained the results given in the table. Assuming that the oxidation in the lungs was normal ($l = 0.05$) we can calculate T as $\frac{100}{95}$ times the oxygen content of the arterial blood before the operation. If the oxygen consumption, D, is 5 volumes per cent, we can estimate α from the equation

$$\alpha = \frac{A - l\,T}{V - l\,T}$$

Oxygen content in arterial blood before and after artificial pneumothorax (collapse of one lung) (after Sackur)

EXPERIMENT NUMBER	OXYGEN CONTENT IN ARTERIAL BLOOD IN VOLUMES PER CENT		ESTIMATED VALUE* OF α FRACTION OF BLOOD PASSING COLLAPSED LUNG	REMARKS
	Before pneumothorax	After pneumothorax		
14	13.6	7.3	0.56	Rabbit, right lung
15	15.3	11.2	0.45	Rabbit, left lung
16	12.3	7.2	0.50	Rabbit, right lung
17	14.3	7.6	0.57	Rabbit, right lung
18	14.4	11.0	0.40	Rabbit, left lung
19	21.5	15.8	0.53	Dog, left lung

* α is calculated by us from equation (4) (page 29) under the assumption that $D = 5$ and $l = 0.05$.

The results which are given in the table show that the estimated fraction of blood passing the collapsed lung is 50, 56, and 57 per cent in the 3 cases, where the right lung was collapsed, and 40, 45, and 53 per cent in the 3 cases (2 rabbits, 1 dog) where the left was collapsed. No definite change took place in the carbon dioxide content of the arterial blood, which in some cases was moderately increased, in others diminished.

If the lung tissue is abnormal, as for instance, in tuberculosis, cyanosis does not often ensue when spontaneous pneumothorax takes place. The reason for this is presumably that α cannot reach a value large enough to cause cyanosis on account of thrombosed vessels so often seen in tuberculous lungs.

In cases where the lung is not only collapsed, but compressed, either by effusion or by artificial (closed) pneumothorax, cyanosis is usually not observed. The reason for this is that in some cases aeration of the lung still takes place to a certain extent; in other cases that the blood flow through the compressed lung is either diminished or prevented by pressure in the pleural sac approaching or exceeding that in the pulmonary artery. In the case observed by Lundsgaard and Möller (b) this latter condition was evidently present. In 4 experiments on animals (rabbit, cat, and goat), Le Blanc found that the arterial oxygen unsaturation increased only slightly after a closed pneumothorax. If no aeration had taken place in the collapsed (compressed) lung, this would indicate that it had been passed by only a small fraction of blood. However, in 2 of his 4 experiments (nos. 1 and 4) some aeration must, as Le Blanc remarks himself, have taken place. In the first instance (experiment 1) he found that an obstruction of the main bronchus after pneumothorax increased the oxygen unsaturation of the arterial blood. After pneumothorax alone, the saturation of the arterial blood was 10.73 volumes per cent. However, when bronchial obstruction was added to pneumothorax, the saturation of the arterial blood went down to 9.16 volumes per cent. This shows that the ventilation of the (right) lung was not entirely prevented by pneumothorax itself. In the second instance, experiment 4, the arterial oxygen unsaturation went up when the amount of air (nitrogen) in the pleura was increased from 750 to 1,100 c.c. In 7 patients with tuberculosis, where the result of the x-ray examination seemed to exclude any lung function of the affected side, Le Blanc found the saturation of the arterial blood to be within normal limits before and after pneumothorax in all instances except possibly in patient no. 2. He (page 59), therefore, concluded that almost no blood had passed the affected lung. Attention should, at this place, be called to Bruns' six (animal) experiments on the content of blood in collapsed or compressed lungs. He found at autopsy that the amount of blood in a

compressed lung was smaller than that in the other lung and that it decreased with the degree of the compression. Further experiments on animals with simultaneous analyses of oxygen content of arterial and venous blood, and observations of intrapleural pressure, would be desirable. If venous blood from the pulmonary artery could be obtained, and if aeration of the compressed lung could be prevented, the fraction of blood (α) passing this lung could be calculated from our formula (4) under the assumption that the oxygenation of the blood in the non-compressed lung was normal (normal l).

B. Heart diseases

In circulatory disturbances cyanosis is a common symptom. It may occur early in the disease, as is often seen in lesions of mitral and particularly of congenital origin. In such cases it is usually associated with respiratory impairment (dyspnea) and is often seen only after exercise. Or, it may be a late symptom associated with definite signs of marked absolute heart insufficiency (stasis and edema). It may, therefore, be encountered in all kinds of advanced heart disease. Our present knowledge of the mechanism of the undoubtedly very complicated circulatory and respiratory disturbances in heart diseases is still so imperfect that it seems impossible to enter successfully into an analysis of the quantitative relationship of the different factors (causative and modifying) which participate in the production of cyanosis. Only suggestions can be made.

A. Congenital heart diseases. We shall not enter into the morphology of the congenital heart lesions. The possibility of the presence of a shunt and its direction as judged from postmortem examination is discussed in several papers of Abbott and her associates. From these papers valuable information about the relation of cyanosis to the varying morphological types may also be obtained. Readers are also referred to Peacock's, Keith's, and Mönckeberg's publications on the morphology of congenital heart lesions. In the very heterogeneous group of heart lesions which includes what are usually called the congenital heart diseases, cyanosis is, as mentioned, often an early and, as indicated by the name "morbus cæruleus," a very prominent symptom. It is, however, not so common as is often believed. Thomson found it only in 53 per cent of 136 cases and

Still describes it in 34 of his 100 observed cases. It is usually, since de Senac (1749), ascribed to a shunt permitting blood to pass unaerated from the veins to the arteries (positive α), although other explanations have been given (stasis, capillary malformations, and polycythemia). These factors include what we have termed *causative* and *modifying* factors, and all may perhaps enter into the formation in these cases. As to the possibility of a positive α in cases of congenital heart disease with cyanosis, we know that an abnormal communication between the right and left side of the heart is encountered in open foramen ovale in defective ventricular septum and in open ductus Botalli. Only in cases of complete fusion of the two ventricles into one, with resulting mixture of the two blood streams, is such a defect in itself sufficient cause for a positive α. In other cases the blood will flow *from left to right* unless, as first pointed out by Corvisart (1818), certain other abnormalities (as for instance pulmonary stenosis) are present, which might increase the pressure in the right ventricle above that in the left or in the aorta. Abbott, in Osler and McCrae's "Modern medicine," 1915, page 359, points out that a dilatation of the pulmonary artery with hypoplasia of the aorta is the rule in uncomplicated cases of widely patent foramen ovale or in large defects of the interauricular septum, and that the same condition exists, though in a lesser degree, in those rare cases of interventricular septal defect uncomplicated by pulmonary stenosis or dextroposition of the aorta. This furnishes, as Abbott points out, anatomical evidence that a considerable amount of blood must have passed from left to right through the abnormal communication. Figure 20 represents the circulatory conditions in a patient when a certain fraction of the blood passes through an abnormal communication from the left to the right side of the circulation. This diagram is constructed on the same basis as figures 12 to 15. In most cases of defective ventricular septum or persistent ductus Botalli, a pulmonary stenosis is present, but whether or not it is sufficient to produce the inversion of the pressure is difficult to decide.

In some cases a mitral lesion, a myocardial insufficiency, or a lung lesion resulting in an increased pressure on the right side of the heart might be the cause of the reversion of the shunt. (Cf. Bard and Curtillet's "Forme tardive de cyanose.") Interesting in this respect

is Carey's report on the clinical and pathological findings in two patients with defective interventricular septum of the heart, one with, the other without cyanosis. One began to show cyanosis at 6 years of age and died from septic endocarditis at the age of 25. Autopsy showed a communication between the right and left ventricle 1.5 cm. in diameter. A marked stenosis of the pulmonic artery was present, and the walls of the right ventricle equaled in thickness

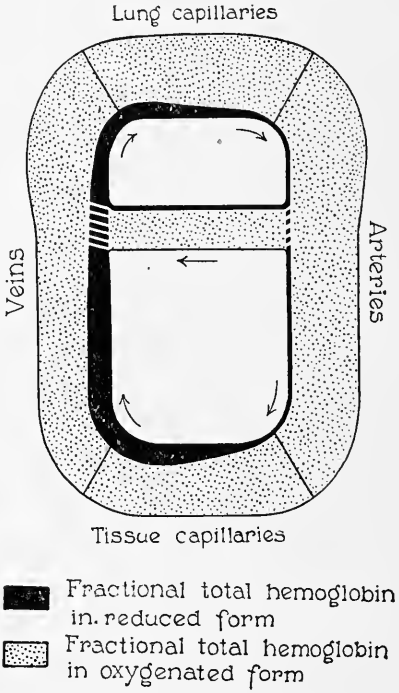

FIG. 20. DIAGRAM SHOWING THE PROPORTION OF OXYHEMOGLOBIN TO REDUCED HEMOGLOBIN IN DIFFERENT PARTS OF THE CIRCULATORY SYSTEM IN A CASE WHERE A FRACTION OF BLOOD PASSES FROM THE LEFT SIDE OF THE HEART TO THE RIGHT SIDE THROUGH AN ABNORMAL COMMUNICATION

the walls of the left. In this case conditions for a right to left shunt great enough to cause cyanosis were presumably present. The absence of cyanosis from birth to the sixth year can be explained in two ways: either by the presence of a left to right shunt during that period, which, of course, would not give rise to increased capillary

unsaturation; or by the passage of an amount of blood from right to left too small to give a capillary unsaturation above the threshold value. In the sixth year one must assume that for some reason or other the shunt had either become reversed, or the α had increased enough to cause cyanosis. The other case was a patient who died at the age of 35 years of mitral insufficiency. At autopsy an interventricular communication of 0.4 cm. in diameter was found. No pulmonic stenosis was present nor any hypertrophy of the walls of the right ventricle. We are justified in assuming that no blood can have been shunted from right to left in this case.

If, in a given case, we can assume that the oxygenation in the lungs is normal ($l = 0.05$), demonstration of an increased unsaturation A of the arterial blood is decisive for the presence of a positive α. If, furthermore, we could determine the oxygen consumption, D, and the hemoglobin content, T, we could estimate quantitatively the size of the fraction. Such data are, however, not available; in fact, the available information is not even quite sufficient to demonstrate qualitatively the presence of an unaerated shunt of venous blood into the arteries. Several valuable investigations concerning the circulation in such cases of congenital heart failure have been published. Plesch determined in 1909 the blood flow in a patient with persistent ductus Botalli, and obtained results which indicated a shunt from left to right. Hürter determined in 1912 the arterial unsaturation in a case of persistent ductus Botalli. At rest, the arterial blood was almost normally saturated, 91 per cent, giving an unsaturation of 1.8 volumes per cent (T was 20.35 volumes per cent). Hürter did not mention any abnormality of the skin color when the patient was at rest, so it is probably justifiable to assume that no cyanosis was present. "Es tritt aber schon bei geringen körperlichen Anstrengungen eine deutliche Cyanose mit Kurzatmigkeit auf." No analysis of the blood was made after exercise. Whether a certain fraction of the blood was shunted through the ductus from the right heart to the aorta during exercise on account of change in the pressure conditions cannot be decided, but at rest no blood could probably have been shunted. Boothby and Abbott proposed in 1916 to differentiate between a left to right and a right to left shunt in patients with congenital heart disease by determining the carbon dioxide tension

(instead of the oxygen tension as done by Plesch) in the arterial and venous blood. In left to right shunt the difference between the arterial and venous carbon dioxide is presumably smaller than in normal individuals, while the opposite is true in a right to left shunt. No determinations where this procedure has been used are published. Hess and Pearce in 1917 estimated the carbon dioxide tension in blood entering and leaving the lungs and obtained results which pointed to an unaerated shunt from right to left. Lindhard (b) made in 1913 a series of determinations of the minute volume in a patient where the postmortem examination, two years later, showed a defect of ventricular septum and a pulmonary stenosis. His results are of great interest, but not absolutely decisive to prove the existence of a positive α. Combined with analyses of the arterial blood, his observations would have made a most complete investigation of the circulation in such a case.

However, in most of the cases of congenital cyanosis, a positive α is presumably present. Other factors of which even less is known may be active in such cases. An increased l may add its effect to that of α, particularly, in later stages where lung involvement may be found. In such cases the influence of l would be magnified by the abnormally high hemoglobin content, T, commonly observed in such cases. The influence of T in magnifying the influence of a large l is shown in equation (9) and discussed on page 33. Also the modifying factors may be changed so that their influence is increased with resulting depression of the threshold of cyanosis or increase of the degree of the color present. Carpenter, in 1890, called attention to an increase in the width and number of capillaries and also to probable formation of new ones. Experiments on animals point in the same direction (Loeb), and Knapp showed in 1861 the increased width and tortuous shape of the capillary vessels in the retina. An increase in the blood volume in such cases has been shown by Bock and Means.

If, in heart failure, slow circulation develops, then increased oxygen consumption per unit of blood flow (increased D) may enter into the group of factors contributing to cyanosis. The effect of D will, as previously shown in equation (9), and discussed on page 36, be magnified by the presence of a positive α. Stasis would, furthermore,

act by increasing at least one of the modifying factors favoring cyanosis, namely, the volume of blood per unit of skin area.

It has been previously mentioned that equation (4) can be used for calculation of α in a given case of right to left shunt.[9] In man such a calculation can be only approximate because when α is positive, l cannot be determined experimentally. By animal experiments, however, it might be possible to throw light on the problem of the mechanism of the circulation in abnormal communication between right and left side of the heart. If a perforation of the ventricular septum could be produced and increasing constriction applied to the pulmonary artery, analyses of oxygen content of arterial blood and of blood from the two ventricles would enable us to calculate α with certainty.

B. Mitral lesions. The common occurrence of cyanosis in mitral and some forms of myocardiac lesions is probably related to the early involvement of the lungs through the increased pressure in the pulmonary circulation. It is therefore natural to ascribe cyanosis mainly to incomplete reoxygenation in the lungs. This viewpoint is sustained by Harrop's determinations of the oxygen in the arterial blood in 4 cases of myocarditis and 2 cases of mitral lesion. He found a moderate increase of the arterial unsaturation in all of them.

[9] The formula which would apply to a left to right shunt is developed as follows:
Let
A = oxygen unsaturation of arterial blood.
V_1 = oxygen unsaturation of venous blood in pulmonic artery after the admixture has taken place.
V = oxygen unsaturation of venous blood before admixture has taken place, that is, for instance, in the right auricle.
D = amount of oxygen taken away from the blood in the tissue capillaries.
β = fraction of blood passing from left to right through short circuit.

$$V_1 = V(1 - \beta) + \beta A \tag{1}$$

or

$$\beta = \frac{V_1 - V}{A - V}$$

therefore

$$\beta = \frac{V_1 - (D + A)}{-D} \tag{2}$$

or

$$\beta = 1 - \frac{V_1 - A}{D} \tag{3}$$

Whether this was due to increased l or to a positive α cannot be decided. The probability that increased l is responsible is indicated by the result of oxygen therapy in a series of cases (Barach and Woodwell, a). They found that administration of oxygen relieved the cyanosis and increased the arterial and venous oxygen saturation. It has previously been pointed out (page 26) that determination of the total blood flow (Means and Newburgh; Lundsgaard, 1916, a and b) and of the local blood flow (G. N. Stewart; Hewlett) also suggests that decreased flow rate may add to the cyanosis by increasing D.

Stasis may add its influence to the lung involvement not only by increasing D, but also, as previously discussed (page 14), by increasing the width and number of blood-filled capillaries, thus augmenting the most important modifying factor. No quantitative figures are, as mentioned, available for estimating the influence of this factor.

C. Aortic lesions. Aortic lesions, including hypertrophy of the left ventricle in patients with hypertension, are rarely associated with cyanosis before advanced stages, when the heart insufficiency is marked. The reason for this is probably that the lungs are usually not often involved during the first stages. Consequently, it appears that in aortic lesions, l and α, the two most powerful factors (see fig. 16) do not come into play at the early stages. For a decreased minute output of the heart alone to cause a cyanosis, through an increased D, the drop in minute output must be great (see fig. 18), unless the effect is reenforced by an abnormal distribution of blood through the action of the vasomotor mechanism, or by that of modifying factors (stasis). In a case of aortic insufficiency with marked decompensation, Hürter found that the arterial blood was only 85 per cent saturated (oxygen unsaturation 2.75 volumes per cent). Assuming normal D of 5.0, this would give a mean capillary unsaturation of $\frac{2.75 + 7.75}{2} = 5.25$ volumes per cent. This is in accordance with the observation that "auffallend war die geringe Cyanose." Harrop examined the blood oxygen in 2 patients (nos. 8 and 9) with aortic insufficiency. Both were slightly decompensated (edema). The lungs were clear in no. 9, and a few crackles were heard at the bases of no. 8. Neither of them was cyanotic. The arterial blood was normally saturated with oxygen (93 to 98 per cent) and the arterial oxygen

unsaturation was from 0.37 to 1.43 volumes per cent. *D* was somewhat increased in both cases, pointing towards a diminished blood flow. In aortic diseases, therefore, cyanosis is usually first encountered in the advanced stages, where lung involvements (and probably increased *l*) may be present.

D. Arrhythmia. There seems now to be sufficient clinical and experimental evidence to support the view first advanced by Wenckebach, Mackenzie, and Thomas Lewis, that an arrhythmic heart condition in itself may cause in some instances diminished output of the heart. This must necessarily result in a slow circulation, and consequently, in an increased *D*. Whether or not the cyanotic attacks observed in such patients can be solely ascribed to such increased *D*, is not known. It is, however, most likely that other factors are in play. An anatomical shunt (positive α) can be excluded. That a slow circulation in itself should cause a diminished reoxidation in the lungs is a priori very unlikely. Barcroft, Bock, and Roughton who examined the arterial blood of a patient with paroxysmal tachycardia found an increase in the degree of oxygenation in the lungs. Meakins (d), who examined 5 patients with auricular fibrillation, did not find any decrease in the oxygen content of the arterial blood except in cases with edema of the lungs. Similarly, Meakins found normal oxygen content of the arterial blood in 4 dogs with experimental tachycardia. H. G. Stewart examined patients before and after they had recovered from fibrillation with the assistance of quinidine therapy. He found arterial unsaturation within normal limits both before and after recovery. In the majority of cases of arrhythmic heart action showing cyanosis, valvular lesions and acute or chronic lung involvements exist, which, as shown by Meakins (d), may influence the pulmonary oxygenation of the blood. The valuable effect of oxygen therapy in 2 such cases was demonstrated by Meakins (d).

C. Cyanosis in patients under general anesthesia

It seems justifiable to ascribe the not infrequent occurrence of marked cyanosis in patients under general anesthesia to decreased reoxygenation of the blood in the lungs (increased *l*) on account of low oxygen tension. The fact that the cyanotic color disappears quickly after removal of the mask, and that cyanosis usually does

not occur when the open drop method is used, points also to this explanation. The flushed skin of anesthetized patients, particularly if ether is used, indicates also that the modifying factors may play an appreciable part. A study of the skin capillaries (the vasomotor mechanism) of patients under general anesthesia would be of considerable interest in this respect as in several other respects. As to cyanosis occurring in patients with the so-called delayed chloroform poisoning, nothing is known. In view of the fact that chloroform is a distinct protoplasmic poison, it seems possible that a functional disturbance of the lung epithelium might also be present in such cases. It would be of interest to study the effect of chloroform on the permeability of the lung epithelium to oxygen and carbon dioxide.

D. Cyanosis in intrauterine life and in the new-born

The question might naturally arise whether or not the mechanism of the embryonic circulation, with its physiologic admixture of venous and arterial blood does not cause cyanosis. It has been (Fouquier) considered a serious obstacle to de Senac's theory that "le fœtus n'est pas cyanosé, quoique les deux sang soient mélangés chez lui." Nothing is, so far as we are aware, known about the natural skin color of the fœtus, but in view of the high value of α necessary to cause an appreciable blue color, it does not seem very likely that a physiologic intrauterine cyanosis exists, at any rate not in the later stages of intrauterine life.

During normal delivery, an intense cyanosis of short duration due to deficient oxygenation might be considered a natural sequence of the change from placental to pulmonary oxygenation of blood which normally takes only a very short time.

In new-born children cyanosis is rarely observed. If it is present, it is probably always a pathological condition although it is supposed that some time (a few days) is required before the circulation adapts itself to the extrauterine life by closing the ductus Botalli entirely (see Bryce). However, even if some blood should be short circuited for some time after birth, cyanosis would probably not occur unless about one-third passed the shunt. Absence of cyanosis shortly after birth does therefore not disprove de Senac's theory. Hayem states that the cutaneous blood is darker during the first days after birth

than later.[10] No gas analyses or remarks about skin color are given by Hayem.

If abnormalities take place at birth, conditions are different; cyanosis is then very easily produced and may reach a very intense degree. It occurs under several pathologic conditions and is especially often seen in prematurely born children. The conditions in such cases are, of course, very favorable for the production of cyanosis. A delayed or impaired lung function may cause increased arterial oxygen unsaturation not only directly by incomplete oxygenation (increased l) but also indirectly by a delay in closing the ductus Botalli. Furthermore, the physiologic polycythemia in the new-born may magnify the effect of increased l. Our information about these conditions is so incomplete that a further discussion seems useless for the time being.[11] If clinical observation was focussed on these problems and combined with determinations of blood gases in such cases, information could possibly be gained which would at least be of great theoretical interest. Studies of the blood gases in the new-born face severe obstacles which, however, might be overcome by changing the usual technique for drawing blood. Venous blood might be obtained from the sinuses of the skull and samples of cutaneous blood might be used for the information usually obtained by analyses of arterial blood (Lundsgaard and Möller, 1922). The effect of oxygen therapy might prove of great value in deciding whether the cyanosis in such cases is mostly due to impaired lung function (increased l) or to a shunt (positive α). About the influence of the modifying factors (filling of capillaries, etc.) in these cases nothing is known.

[10] A sa sortie des capillaires cutanés, il est noir, presque à l'égal du sang veineux, et cette couleur, très accusée chez l'enfant n'ayant encore fait qu'un petit nombre d'inspirations, s'atténue un peu au bout de quelques heures, mais elle persiste pendant les premiers jours de la vie jusqu' à une époque encore indéterminée. Elle est encore plus noirâtre que celle du sang de l'adulte, douze jours après la naissance (Hayem, p. 179).

[11] H. Bakwin has determined, in a number of babies (some prematurely born), the oxygen in venous blood drawn from the sinuses of the skull, before and after oxygen treatment. It was found in several instances that the cyanosis disappeared and the oxygen content of the venous blood was increased after administration of oxygen. This indicates that the blue decoloration in these babies was due to insufficient oxidation of the blood in the lungs (decreased l) and not to a short circuit through the ductus Botalli or through the lungs. No determinations of the oxygen in the arterial blood were made (personal communication added to proof).

E. Polycythemia vera (Vaquez-Osler's disease)

The first observed case of this disease was described by Vaquez in 1892, but "en l'absence de toute autre hypothèse plausible," Vaquez diagnosed it as a case of congenital heart disease with polycythemia and cyanosis, until the postmortem examination a year later disclosed the splenomegaly and the absence of any heart lesions. It so happened that cyanosis went down in the history as one of the cardinal symptoms of Vaquez-Osler's disease together with polycythemia and splenomegaly. Several authors, among them Osler himself, have been inclined to describe the color change in these cases not as a cyanosis, but as a "congestion or ruddiness" of the skin. It has therefore been proposed to term the skin color erythrosis instead of cyanosis (Paltauf).[12]

Hürter determined the arterial unsaturation in a case of polycythemia and found an unsaturation of 1.49 and 3.07 volumes per cent. The last figure is above normal and points towards an increased *l*. The increase in the arterial unsaturation is almost large enough to turn an erythrosis into a cyanosis, even if *D* and the modifying factors are normal. No observations of the skin color are reported by Hürter. Lundsgaard (d) determined the venous oxygen unsaturation in a similar case where the skin color was red. Of 4 determinations the highest value was 6.6, the lowest 5 volumes per cent. Assuming a normal *D*, the arterial blood was normally saturated in this case. However, even if the skin color in Vaquez's disease is red rather than blue, it must be admitted that such patients become very readily, either generally or locally, cyanosed. There appear to be two main reasons for this: the first being the increased hemoglobin content, *T*, which magnifies the influence on capillary unsaturation of *l*. This is discussed and shown in detail on page 33 and following. The second reason is the abnormal state of one of the modifying factors, namely, the condition of the capillaries, the number and width of which may be increased (see page 15). It has furthermore been shown that the state of the capillaries is highly variable, a condition which Thaysen has named capillary ataxia. Information on this is, how-

[12] In 1919 one of us (C. L.) proposed the term erythrosis for the skin color in Vaquez's disease, not knowing that Paltauf had already used this name.

ever, at present too slight to allow any estimate of the relative importance of these two factors in the production of cyanosis. Quantitative studies on the skin capillaries in such cases would be desirable, in combination with determination of the three factors l, T, and D involved in the production of capillary unsaturation in these cases.

F. Anemia

Clinical observations show, as pointed out by Lundsgaard (c), that anemic patients exhibit less tendency to become cyanotic than do normal individuals. This is explained in part by the decreased value of T in such cases (see page 33), in part by changes in the modifying factors due, as pointed out before, to decrease in the number and width of blood-filled capillaries per skin area unit (see page 16). If the hemoglobin content of the blood is less than 30 per cent normal (5 grams hemoglobin per 100 c.c. of blood), cyanosis does not usually appear. However, by applying prolonged stasis (tension below systolic pressure) to the arm of a patient with hemoglobin of 21 per cent, we were able to produce a faint trace of cyanotic color (non-published observation). This is due to the increased influence of the modifying factors which, as previously mentioned, may depress the threshold value of the mean capillary unsaturation at which cyanosis appears. Combined studies of the color changes of the skin following stasis applied under measured pressure, of the oxygen of the blood, and of the number and width of the capillaries, would be instructive. It seems better in such cases to compare the skin color of an arm after stasis with a normal individual than with the pale color of the opposite arm, and it must be remembered that the mean capillary unsaturation in prolonged stasis probably equals the venous unsaturation on account of the back pressure.

G. Cyanosis at high altitudes, mountain sickness

The factor mainly responsible for the production of cyanosis at high altitudes is incomplete oxygenation in the lungs (increased l) due to low atmospheric oxygen tension. Its effect, as pointed out before, may be magnified by the presence of a polycythemia (see page 34 and equation (9)). In normal individuals with $T = 20$ volumes

per cent, and $D = 5$ volumes per cent, one would expect to find that cyanosis would begin at an oxygen saturation of the arterial blood of about 80 to 85 per cent, which would give a mean capillary unsaturation of 6.5 and 5.5 volumes per cent, respectively. This expectation accords, as previously mentioned, with the experience of Barcroft and his party in the Andes. If air with a low partial pressure is inspired, the same effect is seen (Lundsgaard, c). The relief of cyanosis in such cases by breathing oxygen is due to return to normal of the increased unsaturation (l) of the pulmonary blood. We have previously discussed the influence of anemia in hindering the appearance of cyanosis in such cases because with less total hemoglobin (T) present, a given percentage unsaturation (l) produces a smaller concentration of reduced hemoglobin, and less blue color. Other factors being equal, of 2 individuals, 1 polycythemic, the other anemic, the former would show cyanosis at high altitudes more readily, but be nevertheless the better adapted to endure them.

H. Local cyanosis, acrocyanosis

Cyanosis is more often localized than general. The reason for this is that to factors acting generally on the capillary unsaturation (as increased l or positive α), there is added a locally increased D. Furthermore, the modifying factors are usually of more importance in one region than in another. Consequently, in cases of deficient oxygenation in the lungs, we frequently find that the cyanotic color is either confined to, or is most marked at certain places (hands, feet, nose, lips, cheeks, and ears).

In other cases the factors producing cyanosis are of purely local, peripheral nature, so that abnormal skin color naturally is confined to the parts where such factors act. An obvious example of locally produced cyanosis is caused by applying stasis to the arm, or by exposing an extremity to cold. Clinically, local cyanosis is especially often seen at the extremities, and is most marked at the distal parts. For this condition the word acrocyanosis is often used. Such cases are often observed, and the cyanotic color is usually ascribed to nervous influence, to thermic irritation, or to local stasis.

The factors acting in these cases must presumably be: first slow blood flow and consequently increased D, as already suggested by

Raynaud; second, an increase in the influence of two of the modifying factors, namely, the increase in number and width of blood-filled capillaries, and the shape of the capillary reduction curve (see fig. 11), which probably on account of back pressure and blocking of the blood flow would be very abnormal so that the average capillary unsaturation probably would be near V instead of $\frac{A + V}{2}$. Apart from the experiments reported by Lundsgaard (c) and by Meakins and Davies, no information is available as to the blood oxygen in such cases. A closer study would be desirable, but certain difficulties are encountered here. It seems impossible to be certain as to the area drained by the vein from which the blood is drawn. The cubital veins receive blood from the superficial layer of the entire forearm, and probably to a certain, and possibly varying, extent from the deeper tissues. Nothing is known about it. Analyses of blood from the more peripheral and smaller veins would be useful, but have not yet been done.[13] In a study of the oxygen content of the so-called capillary blood from incisions in the finger tip, Lundsgaard and Möller (b) found that blood so obtained was to be looked upon as arterial blood.

As to the influence of the modifying factors, it is, as mentioned, easy to demonstrate qualitatively that the visible skin capillaries of the fingers increase in number and width, and probably also in length, if artificial stasis with cyanosis of an arm is produced. No quantitative and almost no qualitative study has been made of the influence of different pressure levels on the number and width of the capillaries. Such studies combined with careful observation of the degree and distribution of the cyanotic skin color might prove valuable.

Slow blood flow in patients with Raynaud's disease and in other cases of acrocyanosis has been observed directly by capillaroscopy, and increased width and length of the capillaries have been observed (Weiss and Holland; Pribram and Henius; Halpert; Boas; see fig. 10).

[13] Goldschmidt and Light have found that the superficial blood from the back of the hand has a higher percentage saturation of oxygen than the blood drawn from the deeper veins at the elbow. Their study includes the effect of various factors upon the oxygen of these bloods. This work will be published in the near future (personal communication added to proof).

Boas has shown that the capillary circulation in acrocyanosis varied with the clinical condition of the patient. When the fingers were cyanotic and cold, he found a low capillary blood pressure and a sluggish streaming of blood. When the hands appeared normal, or when they were immersed in hot water and became erythrotic, the capillary pressure increased and the streaming became faster.

Bruns and König, and Carrier, have studied by capillaroscopy the influence of application of heat and cold on the skin capillaries in man. The ordinary sequence of events which takes place during a transition from a warm to a cold environment (air or water) is described by Carrier in a publication from Krogh's laboratory as follows: "When the surrounding atmosphere becomes more and more cold, the capillaries and arterioles, which in warmth are open and have an even, rapid stream become contracted. The flow of blood through them becomes very much reduced and the skin is white. Further cooling, however, paralyzes the capillaries so that they relax. For a time there is enough blood coming through the contracted arterioles to give a slow arterial stream in the capillaries; but, as the cold becomes more intense, the arterioles are so completely contracted that the flow of blood stops. The open capillaries fill with venous blood and the skin is cyanotic." It is clear that both the causative and modifying factors are involved in producing the cyanotic color of the type described by Carrier. So far we are unable to judge about the quantitative influence of the two factors in such cases. It seems probable that much information regarding the undoubtedly very marked influence of the modifying factors on the appearance and degree of acrocyanosis might be obtained by a further study of the influence of different stimuli (mechanical, thermic, electrical, and chemical) on the condition of the skin capillaries in cyanotic and non-cyanotic individuals.

HISTORIC DEVELOPMENT OF THEORIES OF CYANOSIS

Much clinical material on cyanosis has been published. More than 500 publications have appeared since the time of de Senac. Most of these are in casuistic form, but quite a few are monographs or dissertations. In most of the publications that have been accessible to us, the authors have, besides reporting their material, entered into dis-

cussion of the theories of cyanosis. These theories are of considerable interest for several reasons. First, because the two most important of them were created by de Senac and Morgagni, from the two first well observed cases. In spite of the fact that these two men observed only one case each,[14] they created from their observations theories which in the main still hold good when they are interpreted in the modern language. Second, because the variations in the conceptions of the cause of cyanosis are very intimately connected with the leading viewpoints in medical science as a whole.

In the following we shall very briefly give an account of the theories of cyanosis. We shall pay most attention to the historic background for these theories, less to the discussion pro and con. The theory holding an admixture of venous and arterial blood to be a cause of cyanosis will, however, be discussed in more detail. We have reserved the historical review for the conclusion of our paper in the belief that after the reader has read an exposition of the causes of cyanosis, as revealed by the methods of modern physiology, he may be in a better position to appreciate the mental keenness with which some of the early clinicians interpreted their observations.

As is known, de Senac (1749) was the first to advance a theory concerning the cause of cyanosis. He thought it was due to an admixture of venous and arterial blood through the heart. A few years later (1761) Morgagni suggested pulmonary stenosis as the cause. He thought that a stenotic condition of the valves caused stasis and cyanosis as well. Although the validity of de Senac's theory was supported by observations of cyanosis in patients in whom conditions for an admixture of venous and arterial blood were present, his theory was nevertheless repeatedly challenged because anatomical conditions for the admixture of venous and arterial blood were observed without the occurrence of cyanosis.

In 1823 Louis in a critical discussion of 20 cardiac cases, partly from

[14] de Senac reports a case of chronic cyanosis in a man, twenty-seven years of age, in whom at autopsy the two ventricles were found to be united into one. Morgagni's case is a girl, sixteen years of age, who had been cyanotic since birth. At autopsy, marked pulmonary stenosis and open foramen ovale was found. The condition of ductus Botalli is not mentioned.

the literature and partly observed by himself, reached the following conclusion (page 341):

"Il est donc impossible, soit qu'on s'appuie sur le raisonnement ou sur l'expérience, de soutenir que la couleur bleue soit un effet du mélange du sang noir et du sang rouge, d'autant plus que d'après ce qui a été dit, ce mélange paraît avoir lieu à un degré plus ou moins marqué dans tous les cas, et que néanmoins, au rapport des auteurs, et d'après les observations que nous avons citées, la couleur bleue est loin d'être constante et surtout générale (obs. IV). Ajoutons, comme le remarque M. le professeur Fouquier, à la suite de l'observation recueillie par M. Thibert, que la peau du foetus où ne circule que du sang noir, n'est pas bleuâtre.

"L'impossibilité d'expliquer la couleur bleue dans les cas dont il s'agit, par le mélange des deux espèces de sang, étant bien démontrée, il faut considérer les faits sous un autre point de vue. Morgagni nous semble avoir donné la véritable explication de celui qui nous occupe, dans le commentaire de l'observation que nous lui avons empruntée. Pour se rendre compte de la couleur livide dont il s'agit, il remarque que le rétrécissement de l'orifice de l'artère pulmonaire, par suite d'une ossification qu'il croit congénitale, devait causer un grand embarras dans la circulation du sang; que celui-ci restait en stagnation dans le ventricule droit, l'oreillette correspondante et par suite dans tout le système veineux, d'où résultait la couleur livide de la peau. Cette explication nous semble d'autant meilleure, qu'on ne saurait en donner une autre de la coloration bleue qu'on observe si souvent dans l'anévrisme des différentes cavités du cœur."

In 1824 Gintrac analyzed 53 cases of cyanosis from the literature. He found that in some instances conditions for admixture of venous and arterial blood occurred without cyanosis. He did not, however, consider this an obstacle to the adoption of de Senac's theory because, as stated first by Corvisart, certain abnormal pressure conditions, often caused by pulmonary stenosis or other obstacles to the circulation, usually must be associated with congenital malformations of the heart in order to force blood from the right ventricle to the left or from the pulmonic artery to the aorta through the ductus Botalli. A few cases of babies, where the aorta was found to come from both ventricles without causing any cyanotic color, he tried to explain by assuming that the venous and arterial blood differed less at birth than later.

Bouillaud, who in his article in "Dictionaire de médicine et de chir-

urgie pratiques" (1831) explains cyanosis entirely by admixture, admits later on (1835) that the objections, especially of Louis and others, are much against the mixture theory. He admits, furthermore, that admixture cannot explain the cyanosis in venous congestions (aneurisms of the heart). Still he thinks that admixture must be of importance (page 572); "Quant à nous, il nous paraît toujours probable que le mélange du sang noir avec le sang rouge peut contribuer à la production de la cyanose; mais ce mélange a lieu, peut-être, plus rarement qu'on ne l'avait cru jusqu'ici."

After exhaustive analysis of 80 cases of morbus cæruleus which at that time were available in the literature, Moreton Stillé (1844) reached the following conclusions (pages 30 to 41):

"1. That cyanosis may exist without admixture of venous with arterial blood. 2. That there is no proportion between cyanosis, and the degree to which the blood is mixed. 3. That complete admixture of the blood may take place without cyanosis. 4. That contraction of the pulmonary artery is present in every case of cyanosis. 5. That it never exists without the concurrence of cyanosis. 6. That it is an adequate explanation of the most important phenomena of the condition."

Breschet described a case with the left subclavian artery arising from the pulmonary vein and still no cyanosis of the left arm existed. For that reason he did not consider admixture of venous and arterial blood a cause of cyanosis. Niemeyer in his pathology also stated that (congenital) cyanosis is caused by stasis although he admitted that some other cause must be present (page 328):

"Dass die bedeutende Cyanose der Kranken mit angeborenen Herzfehlern einen besonderen Grund hat, ergiebt sich auch aus dem Umstand, dass Kranke mit angeborener Cyanose weit später hydropisch werden als Kranke mit aquirirter Cyanose. Hinge die Cyanose nur von der Stauung ab, so würde dies nicht der Fall sein."

Grisolle (page 416) makes the following remarks about the pathogenesis of cyanosis (in morbus cæruleus):

"Deux opinions ont été émises sur la cause de la coloration bleue, qui est un des phénomènes prédominants de la maladie. Corvisart, M. Gintrac, l'attribuent au mélange des deux sangs; Ferrus et M. Louis l'expliquent

plutôt par la gêne considérable de la circulation. Cette dernière opinion nous semble être la seule admissible. Pour réfuter la premiere, il nous suffra de dire qu'on a vu la cyanose manquer dans les cas où l'aorte naissait du ventricule droit, ou bien encore lorsque le cœur n'était constitué que par une oreillette et par un seul ventricule. Enfin, comme l'a remarqué fort judicieusement le professeur Fouquier, le fœtus n'est pas cyanosé, quoique les deux sangs soient mélangés chez lui. La couleur cyanique s'explique par la gêne de la circulation dépendant du vice primordial de conformation du cœur et des lésions qui l'accompagnent le plus souvent, comme le rétrécissement des orifices, la dilatation des cavités et l'hypertrophie des parois, lésions qui forcent le sang à stagner dans les capillaires de la peau."

These examples show that the fact that conditions for admixture of venous and arterial blood have been found without cyanosis has been one of the most serious objections to de Senac's theory of cyanosis.

That the concentration of reduced hemoglobin in the skin capillaries must *reach a certain grade* before visible cyanosis results, makes it understandable that the blue color is not always present, even when there is reason to believe that blood actually passes through the unaerated channels from the right heart to the side, present in patients with deficient ventricular septa or with patent ductus Botalli.

To de Senac and his followers for a hundred years the physiological facts were not available to make possible the conception of oxygen deficit or reduced hemoglobin in the blood as the cause of cyanosis. To them the venous and arterial blood meant two different species with a qualitative, essential difference, clearly expressed by Claude Bernard in a sentence in his lecture on the color of the blood (11th leçon, page 253):

"Cependant, nous pensons que cette distinction, fondée sur la coloration du sang, est loin d'être aussi absolue et d'avoir la signification qu'on a voulu lui donner, en supposant que le sang rouge est un sang doué de certaines propriétés et que le sang noir est doué de propriétés toutes différentes."

In view of the vague conception of the difference between arterial and venous blood, and of the absence of a tradition of quantitative thinking, it is readily conceivable that qualitative evidence carried weight

against de Senac's theory. The existence of cases in which no cyanosis was seen in spite of the fact that the anatomical conditions were present for admixture of venous blood to arterial seemed conclusive against it. That the admixture of a certain *proportion* of venous blood with arterial would be required to cause cyanosis did not enter into contemporary reasoning.

Any causative connection between the blood gases and the cyanotic color could, of course, not develop before it was shown that oxygen and carbon dioxide were present in the blood. It was not until 1837 that Magnus proved even the existence of the blood gases. The importance of this discovery is best elucidated by quoting Magnus (page 188):

"On avait jusqu'à présent préféré admettre que l'acide carbonique se formait dans les poumons plutôt que par l'action des vaisseaux capillaires, parce que l'on n'avait pas encore démontré sa présence dans le sang; à cela se joignait une altération chimique qu'il éprouvait dans les poumons, son changement de couleur. Et cependant c'est un fait bien connu que le sang devient plus foncé en absorbant de l'acide carbonique. Ce changement de couleur pouvait donc s'expliquer par le dégagement de ce gaz. . . . . Certainement, en le purgeant de son acide carbonique, le sang ne devint jamais d'un rouge aussi clair que le sang artériel; mais il paraît d'ailleurs que l'absorption de divers gaz y produit des colorations diverses. . . . . Il est donc vraisemblable que le sang artériel doit sa couleur rouge à ce qu'il s'y trouve moins d'acide carbonique et à l'absorption de l'oxigène."

The qualitative difference between the venous and arterial blood as to the blood gases was first clearly given in 1859 by Claude Bernard (page 290, 13th leçon) who defines venous blood as follows; "en quoi consiste la vénosité: c'est une propriété en vertu de laquelle le sang a changé de couleur et est devenu plus capable d'absorber l'oxygène." It is natural that the cyanotic color in the following period was attributed not to the venous blood in general but to abnormalities in the blood gases. Through analyses of the blood in suffocation the "Venenblut in höchster Potenz" (see Zuntz, 1882, p. 42), a decrease in oxygen and increase in carbon dioxide were found. In local stasis with cyanosis and in cyanotic heart patients (Kraus, 1897, pp. 20 and 36) an increase in the carbon dioxide content of the blood was

found. It seems, therefore, natural that discussion might arise as to which of these abnormalities cyanosis should be ascribed, although physiologists, have definitely shown that the color change of the blood is due, not to alterations in the content of the carbon dioxide, but to changes in the oxygen saturation of the hemoglobin.

Another factor, the importance of the increased number of red blood corpuscles, entered into the discussion of the cause of cyanosis after Toennissen's discovery of polycythemia in heart disease (1881), and particularly since Krehl's observations of marked polycythemia in a patient with morbus cælureus (deficient ventricular septum) in 1889, and Vaquez's description (1892) of a patient with polycythemia vera and cyanosis. This factor was considered, at any rate, mainly responsible for the cyanosis in several of these cases. Some confusion has been introduced because the difference between the red color usually present in polycythemia (erythrosis) and the blue cyanotic color was not clearly defined.

It has been pointed out in this paper that an increased hemoglobin concentration causes a given fall in arterial oxygen tension to produce a greater concentration of reduced hemoglobin, and thereby causes more intense cyanosis.

Morgagni's theory proposing stasis as the cause of cyanosis has played an important part. That stasis is one of the remote secondary causes of cyanosis is very easily demonstrated. Furthermore, stasis and cyanosis are often united in the same patient, particularly in cardiac disease. Cyanosis in other conditions, such as emphysema, asthma, and pneumonia, is difficult to explain by stasis; but even in such conditions the other possible factors have been neglected, with an influence on therapy which cannot in all cases have been helpful.

This short historical sketch is sufficient to show that what we have considered the *cause* of cyanosis; the oxygen unsaturation of the capillary blood, corresponds fairly well to de Senac's theory of the importance of admixture of venous and arterial blood. Similarly, what we have termed the main *modifying factor*, the filling of the capillary bed, is in the main covered by Morgagni's theory that cyanosis is produced by peripheral stasis. The magnifying effect of the hemoglobin concentration in the blood on inefficient oxygenation in the lung capillaries gives the physiologic explanation of the impor-

tance of the increased number of red blood corpuscles of polycythemia in the production of cyanosis. And the modifying factors cover the idea that new formation of capillaries played a rôle in the production of the color in cyanotic patients. Each of these theories of the past contains, so far as we are able to see, a part of the truth, and none of them contains the whole truth.

The different factors, causative and modifying, entering into the production of cyanosis, are in a given case of different quantitative importance. A full analysis of the bedside observation is not always possible, but for the understanding of the observation and the treatment of the patient it is of importance to carry the analysis in every single case as far back as possible to the physiologic and morphologic components of the condition.

SUMMARY

On the basis of Lundsgaard's demonstration that the cause of cyanosis is an abnormally large amount of reduced hemoglobin in the capillary blood, the quantitative effects of four factors contributing to this cause have been estimated, viz., (1) the total hemoglobin content, (2) the degree of oxygen unsaturation of the arterial blood coming from aerated lung areas, (3) the proportion of blood passing from right heart to left through unaerated channels, and (4) the oxygen consumption in the capillaries.

There are various other factors which modify the coloration. Such are local skin vascularity, pigmentation, thickness of epidermis; and also the fact that the mean capillary content of reduced hemoglobin, $\frac{1}{2}(A + V)$, only approximately represents the average content. With changing conditions the latter may, instead of being midway between venous and arterial, approximate either more nearly than the other. The effect of these modifying factors is to cause the mean capillary concentration of reduced hemoglobin at which cyanosis becomes perceptible to vary from 4 to 6 grams of reduced hemoglobin per 100 c.c. of blood, and perhaps sometimes even more widely, although it appears usually to lie near 5.

The main clinical conditions in which cyanosis is a symptom have been considered in connection with the causative and modifying factors present, and attempts have been made to estimate the functional and anatomical significance of the cyanosis in these conditions.

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